Understanding Mechanisms of Acquired Resistance to BIBW2992

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Title: Understanding mechanisms of acquired resistance to BIBW2992: a pilot study

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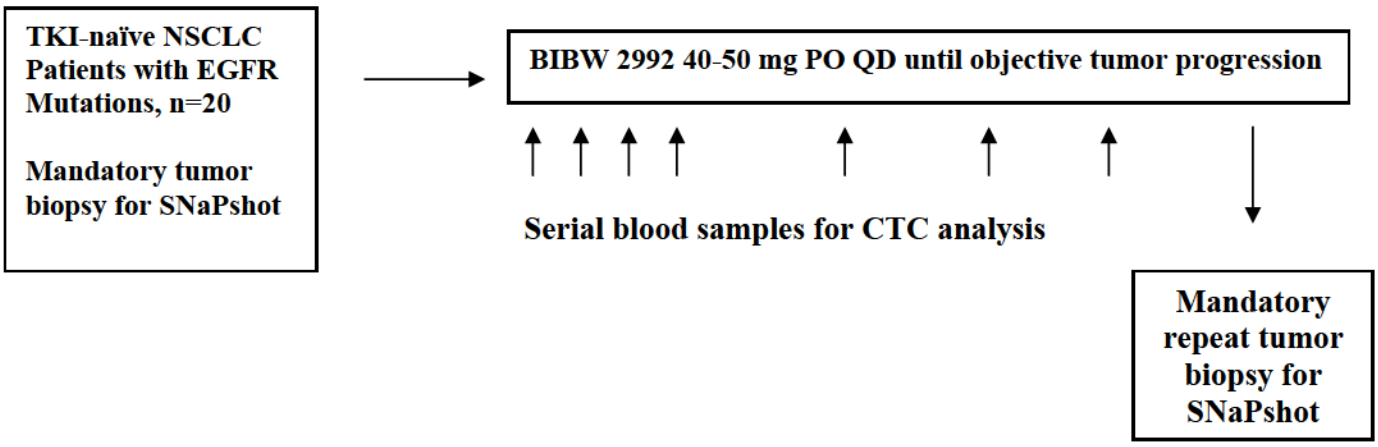
SCHEMA


TKI-naïve NSCLC Patients with EGFR Mutations, n=20
Mandatory tumor biopsy for SNaPshot
BIBW 2992 40-50 mg PO QD until objective tumor progression
Serial blood samples for CTC analysis
Mandatory repeat tumor biopsy for SNaPshot

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1. OBJECTIVES

1.1 Study Design

This is a pilot study examining the feasibility of using a molecular endpoint, specifically acquisition of the T790M EGFR resistance mutation, as the primary endpoint for a clinical trial. The study will consist of 20 tyrosine kinase inhibitor (TKI)-naïve patients with mutations in the epidermal growth factor receptor (EGFR). Patients will be treated with the irreversible pan-ErbB TKI compound BIBW 2992, which in pre-clinical studies inhibits the acquired resistance T790M mutant allele and therefore has the potential to delay the emergence of this common resistance mechanism. However, it remains unknown if BIBW 2992 can overcome the T790M mutation in patients. All patients will initially be treated with BIBW 2992 at 40 mg daily, though as in other studies with this compound, dose escalation to 50 mg will be permitted for individual patients after one cycle if there are minimal adverse events at 40 mg. Patients will continue BIBW 2992 until progression, and tumor tissue biopsy for comprehensive genomic profiling is mandatory at the time of acquired resistance. The primary endpoint will be to determine the proportion of patients with T790M resistance mutations at the time of progression. Serial analyses of circulating tumor cells (CTCs) will also be performed to explore the utility of this platform to assess evolving cancer cell genotypes as resistance develops.

1.2 Primary Objective

1. To determine the proportion of patients that have a T790M mutation on their progression biopsy and to compare this with published data for first-generation EGFR tyrosine kinase inhibitors

1.3 Secondary Objectives

1. To estimate the response rate
2. To estimate the progression-free and overall survival
3. To describe the safety of obtaining repeat tumor biopsies for genotype analysis
4. To describe other mechanisms of resistance (besides T790M) observed on the progression biopsies
5. To explore the results of experimental CTC-derived genotype assessed from serial blood samples taken during therapy with BIBW 2992 and to compare CTC-derived results with those from the progression biopsies

2. BACKGROUND

2.1 Study Agent

2.1.1 Scientific Background

BIBW 2992 is a highly selective and potent low molecular weight, irreversible inhibitor of the erbB-family of tyrosine kinase receptors EGFR (erbB1 / HER1) and HER 2 (erbB2). The potency of BIBW 2992 was determined in enzymatic assays using recombinant human wild-type EGFR (IC50 0.5 nM) and HER2 (IC50 14 nm) (ref. investigator's brochure). A panel of recombinant human kinases tested in parallel was not inhibited, demonstrating the high target specificity of BIBW 2992. Molecular

modeling revealed that BIBW 2992 binds covalently and with high affinity to Cys773 within the catalytic cleft of the ATP-binding pocket of the EGF receptor. It has been reported that this specific molecular interaction results in irreversible inhibition of the EGFR tyrosine kinase domain.[1] Experimental data from *in vitro* washout studies confirmed the irreversible binding of BIBW 2992 to its molecular target. In constitutively EGFR-overexpressing A431 human epidermoid cancer cells, BIBW 2992 inhibition of EGFR-signaling lasted for up to 7 hours after removal of the compound from the cell cultures (ref. investigator's brochure). In contrast, A431 cells exposed to reversible EGFR TKIs regained full receptor function almost immediately after inhibitor washout.

The efficacy and potency of BIBW 2992 was demonstrated *in vitro* in receptor phosphorylation and cell proliferation assays in various human cancer cell models.[2]

The specific activity of BIBW 2992 was determined in two independent *in vitro* assay systems: i) EGF-induced EGFR autophosphorylation using immunoprecipitation and Western blot and ii) clonogenic, anchorage-independent cell growth in a soft-agar assay system.[2] The antiproliferative effects observed with BIBW 2992 compare favorably to activity data published for gefitinib in the same NSCLC cell models.[3] In addition, BIBW 2992 suppressed EGFR phosphorylation and clonogenic growth in the gefitinib resistant NCI-H1975 model, suggesting that tumour cells harboring the T790M EGFR TKI resistance mutation remain sensitive to this irreversible EGFR small molecule inhibitor.[4]

In vitro activity of BIBW 2992 in human cancer cell models is noted in Table 1 below.

Table 1 ***In vitro* activity of BIBW 2992 in human tumour cell models expressing wild type or mutated EGFR**

Cell line	Origin	EGFR status	BIBW 2992 IC50		Gefitinib IC50	
			EGFR-phos-phorylation[1]	Proliferation *in vitro*[2]	EGFR-phosphorylation[1]	Proliferation *in vitro*[3]
NCI-H1666	NSCLC	Wild-type	7 nM	16 nM	100 nM	4 µM
NCI-H3255	NSCLC	L858R-mutation	6 nM	0.7 nM	50 nM	63 nM
NCI-H1975	NSCLC	L858R-mutation and T790-resistance mutation	93 nM	99 nM	resistant	resistant

1 EGF induced auto-phosphorylation of EGFR
2 clonogenic anchorage-independent soft agar assay
3 MTS assay (R06-1388)

The *in vivo* activity of BIBW 2992 against EGFR was investigated in an A431 subcutaneous xenograft model (ref investigator's brochure). Daily oral treatment with BIBW 2992 at doses of 20 mg/kg resulted in an almost complete inhibition of tumor growth over a period of 25 days. Similar anti-tumor activity was observed in NCI-N87 tumor bearing mice treated with BIBW 2992 at similar concentrations. In these *in vivo* studies, BIBW 2992 plasma concentrations of 80-285 nM corresponding to an AUC0-24 of 589-3198 nM*h were required for anti-tumor activity. All BIBW 2992 doses shown to be effective in mouse xenograft models were well tolerated.

2.1.2 Pharmacology and Toxicology Profile

The absolute bioavailability of BIBW 2992 after oral ingestion was 45% in rats with a median t_{max} reached after 4 hours and a terminal half-life (t1/2) of 4.5 hours. In rats the exposure was dose proportional and no gender-related effects or compound accumulation was observed. BIBW 2992 is primarily excreted via the feces. No relevant inhibition of cytochrome P450 isoenzymes was found. *In vitro* BIBW 2992 is however a CYP3A4 substrate. Since this is not considered a dominant metabolic pathway, *in vivo* drug-drug interactions with CYP3A4 inducers or inhibitors are not expected (ref investigator's brochure).

In vivo BIBW 2992 was metabolized only to a minor extent and the metabolism was governed by adduct formation to proteins or nucleophilic small molecules. It was found that metabolism is of subordinate role for BIBW 2992 and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of BIBW 2992 *in vivo*. Only approx. 2 % of the doses were metabolized by FMO3 *in vivo*. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers. Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications)

effects on the activity of FMO3 or CYP3A4 *in vivo* are expected to be of little, if any, relevance for the pharmacokinetics of BIBW 2992.

The human ADME data confirmed the results of the preclinical [^{14}C] ADME studies and all metabolites of the human [^{14}C] ADME study were observed in the rat or the minipig. In acute toxicology studies, oral administration of single doses in rats and mice indicated a low acute toxic potential of BIBW 2992. Changes in renal and hepatic function occurred only at doses that were 10-30 fold above the levels required for antitumour activity. BIBW 2992 had effects on gastrointestinal function that were dose-dependent and in high doses, leading to profound inhibition. No acute toxic effects on the central nervous system were detected.

In oral repeated dose studies for up to 26 weeks in rats and minipigs, the main target organs were the gastrointestinal tract (rats and minipigs), kidneys (rat), and the skin (rats). In the gastrointestinal tract, increasing systemic exposure was associated with dose-dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomach of rats and minipigs. Clinically this resulted in diarrhea in both species and fecal occult blood in a single minipig. In rat kidneys papillary necrosis and dilated tubules were found. Similar pathologic findings, i.e., papillary necrosis in rats and dogs have been described previously for the EGFR-small molecule inhibitor gefitinib. However, nephrotoxicity has not been reported as a side-effect of gefitinib therapy in humans. A secondary pathophysiologic effect on renal function in BIBW 2992-treated animals due to diarrhea-induced dehydration and emaciation has to also be considered. Cutaneous alterations, i.e., epithelial atrophy were observed in rats. However, BIBW 2992 is not irritating to intact skin in albino rabbits and the effects observed in rats are most likely related to the specific pharmacodynamic mechanism of EGFR-inhibition (ref investigator's brochure). A variety of organs including the aerodigestive tract and reproductive organs were affected by epithelial atrophy. These atrophic changes were not severe and fully reversed during a 2-week recovery period. Minor cardiovascular effects (increased blood pressure and heart rate) and a dose-dependent decrease of QT time in the electrocardiogram (ECG) occurred in BIBW 2992-treated minipigs. These data no not indicate a risk for QT-prolongation related arrhythmia. BIBW 2992 had no pro-arrhythmic potential, as determined by the effects on HERG-mediated potassium current or on guinea pig papillary muscle action potential configuration. BIBW 2992 demonstrated mutagenic potential in bacteria but had no genotoxic potential *in vivo* even at highly toxic/lethal doses in animals. Because of its specific pharmacodynamic mechanism of action, BIBW 2992 is potentially embryo/fetotoxic and/or teratogenic.

2.1.3 BIBW 2992 Clinical Trial Program

The most up to date trial and safety information can be found in the current version of the Investigator Brochure.

BIBW 2992 showed moderately fast absorption with median t_{max} values between 1 h to 6 h after administration. The gMean terminal half-life ($t_{1/2}$) of BIBW 2992 mainly ranged between 13 h to 57 h. In general, the maximum blood concentration (C_{max}) and the integral of the concentration time curve (AUC) of BIBW 2992 increased in a dose-proportional way.

The maximum tolerated dose (MTD) of BIBW 2992 was identified as 50 mg once daily in phase I continuous dosing monotherapy trials. The 50 mg dose is currently used in the phase IIb/III trial 1200.23 in NSCLC patients progressing on erlotinib or gefitinib, as maximum EGFR inhibition is required in this last-line population enriched for the presence of resistance mutations. For a more

sensitive population with EGFR activating mutation, a starting dose of 40 mg is expected to be sufficient. In phase I clinical trials of BIBW 2992, durable responses (>20 months) were seen at daily doses of 40 mg and less.

In this trial, a starting dose of 40 mg will be used in order to optimize the efficacy/toxicity balance in the very sensitive population of TKI-naïve patients with EGFR mutations. Variability is expected in the incidence and severity of adverse events and to ensure maximum EGFR inhibition, dose escalation to 50 mg will be allowed after the first course of treatment (28 days) in patients with minimal treatment-related adverse events. This dose escalation strategy has been used before, particularly in the ongoing large international phase III randomized trial of BIBW 2992 versus chemotherapy in patients with EGFR mutations (LUX-Lung 3).

The Adverse Events (AEs) observed to date in Phase I and Phase II trials are consistent with those reported for other EGFR tyrosine kinase inhibitors (dose dependent diarrhea and skin-related adverse events including rash and acne). Other AEs were in the expected range for patients with advanced cancer disease (ref investigator's brochure). In the BIBW 2992 Phase I monotherapy trials, the most frequent drug-related adverse events were associated with gastrointestinal disorders (diarrhea, nausea, vomiting, stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, and acne), general disorders and administration site conditions (fatigue, mucosal inflammation), respiratory disorders (epistaxis, typically grade 1), and metabolism and nutritional disorders (anorexia, dehydration).

Diarrhea is the single most often reported gastrointestinal AE. An increased incidence of diarrhea grade 3 has been observed in phase II monotherapy trials (starting dose of 50 mg qd). Prompt and proactive management of diarrhea together with timely treatment pause and dose reduction is crucial to reduce the severity of diarrhea and its potential complications such as dehydration leading to serum electrolyte changes (hyponatraemia, hypokalaemia and hypomagnesaemia) and/or renal impairment.

Nausea and vomiting are the other commonly reported gastrointestinal adverse events and can be generally managed successfully with the use of antiemetics.

Skin related adverse events present in a number of forms, i.e., rash (including erythematous, maculo-papular, papular, etc.), acne, dermatitis acneiform, dry skin, skin reaction and pruritis. Folliculitis as well as nail changes (including paronychia) are other reported manifestations of skin-related adverse events with BIBW 2992. Early and adequate management of skin-related adverse events can reduce the frequency and the severity of them.

Further AEs included oral discomfort (stomatitis, mouth ulceration, oral pain, dry mouth, soft tissue disorder) and mucosal inflammation. Conjunctivitis and rhinorrhea as a result of inflammation in the mucosal membranes have been reported. Mucosal and skin dryness can lead to epistaxis, which has to date been observed at CTCAE Grade 1. Anorexia, fatigue and asthenia are also frequently observed.

Of 22 evaluable patients with NSCLC from Phase I trials with BIBW 2992, there have been four partial responses (PRs) (3 confirmed and 1 unconfirmed PR) ranging in duration from 5 months to 24 months. All 4 patients were non-smoking Caucasian with adenocarcinoma of the lung. In two of these three patients with confirmed PR, EGFR sequencing has shown exon 19 in-frame deletions.

The efficacy and safety of BIBW 2992 in NSCLC patients with EGFR mutations is under evaluation in a phase II trial (LUX-Lung 2). In this trial, patients with Stage IIIB/IV lung adenocarcinoma with

EGFR mutation in exons 18-21 and failure of one line of systemic chemotherapy were treated with BIBW 2992 at a dose of 50 mg once daily until disease progression.[5] The trial underwent two major amendments. The first was to decrease the starting dose to 40 mg once daily and the second was to allow inclusion of chemotherapy-naïve patients. 129 patients were enrolled. Preliminary results were presented in August 2009 at the World Congress on Lung Cancer. The response rate was 63% in the first-line patients and 66% in the second-line patients. Diarrhea and skin-related adverse events have been the main side effects but have been manageable with appropriate dose interruption/reduction. The incidence of grade 3 diarrhea was lower at 40 mg (4.3%) than at 50 mg (30%). Survival data are not yet mature for analysis.

A global, randomized, phase III trial (LUX-Lung 3) is currently ongoing and is assessing the progression-free survival difference between first-line BIBW 2992 and first-line chemotherapy with cisplatin and pemetrexed in NSCLC patients with EGFR mutations.

2.2 Study Disease

2.2.1 Non-Small Cell Lung Cancer, EGFR Mutations, and Tyrosine Kinase Inhibitors

Non-small cell lung cancer (NSCLC) is the most common cause of cancer mortality in men and women in the U.S. Approximately 170,000 Americans will be diagnosed with NSCLC this year and approximately half of them will have advanced or metastatic disease at presentation, which is not curable. Chemotherapy and biologically targeted agents can extend survival modestly for these patients; however, discovery of novel ways to prolong the disease course is a top research priority.

The epidermal growth factor receptor (EGFR) signaling pathway plays a central role in the neoplastic transformation of NSCLC and promotes cancer cell survival, metastasis, and angiogenesis. The predominance of EGFR signaling in NSCLC makes the pathway an attractive candidate for the development of targeted therapeutics. In the last six years, the FDA has approved two drugs in this class for salvage treatment of NSCLC, gefitinib (Iressa ®, formerly known as ZD1839) and erlotinib (Tarceva ®, formerly known as OSI-774). Both are small molecule orally-bioavailable tyrosine kinase inhibitors (TKIs) of the EGFR TK domain. Erlotinib improves survival compared to placebo when administered after failure of first line or second line chemotherapy for advanced NSCLC and is currently approved for that indication.[6] Gefitinib received accelerated approval for salvage treatment of NSCLC based on response to treatment and symptom improvement in phase II clinical trials. A randomized placebo-controlled trial failed to demonstrate a survival benefit and gefitinib is now only available in the US if participating in a clinical trial, though it is widely used elsewhere in the world.[7]

Our group and others described somatic mutations in the *EGFR* gene that sensitize NSCLC tumors to TKIs, present in about 10% of unselected US patients with NSCLC but in up to 50% of never-smoking NSCLC patients.[8-11] Activating EGFR mutations primarily consist of overlapping deletion mutations in the LREA region of exon 19 or the point substitution mutation L858R in exon 21, though there are several other rare activating mutations described in the literature.[12] EGFR mutations confer a state of "oncogene addiction" on the molecular biology of the tumor, such that the critical downstream signaling pathways are solely controlled by EGFR and are therefore highly susceptible to cell death by blockade of EGFR.[13, 14]Our group has previously demonstrated that patients with advanced NSCLC and EGFR mutations treated with first-line gefinitib have a median progression free survival of 9.2 months, and median overall survival of 17.5 months. [15] This study is consistent with other trials using EGFR-TKI treatment in patients with mutations, which demonstrate response rates >50% and time to progression of >9 months [16-20]

Such a "genotype-directed" treatment strategy has now been proven effective in 2 randomized trials. The IPASS study was conducted in Asia where EGFR mutation incidence is higher.[21] All patients were non-smokers or former light smokers (quit at least 15 years prior and ≤ 10 pack years history) and all had newly-diagnosed advanced adenocarcinoma. Patients were randomly assigned to front-line gefitinib or front-line chemotherapy with carboplatin and paclitaxel. The study utilized a non-inferiority design powered to demonstrate that the 95% confidence interval (CI) for the hazard ratio (HR) for PFS of gefitinib compared to chemotherapy lay entirely below the target of 1.2. The overall PFS HR was 0.74 (95% CI 0.65-0.85), showing that gefitinib was not only non-inferior, but was actually superior to chemotherapy. Even more illustrative was the molecular sub-group analysis. EGFR mutation status was available for 36% of patients and the mutation-positive rate was 60% in this clinically-enriched study. For mutation-positive patients the results favored geftinib even more strongly, with a PFS HR of 0.48 (95% CI 0.36-0.64). Conversely, for mutation-negative patients, chemotherapy was a better treatment with a PFS HR of 2.95 (95% CI 2.05-3.98). In other words, for patients known to harbor an EGFR mutation, gefitinib was more effective than carboplatin and paclitaxel with regards to PFS, but for patients who fit the "clinical phenotype" of a TKI-responder, the genotype trumped the phenotype and TKI therapy did not have a good outcome. This landmark study argues that patients with a moderate chance of harboring an EGFR mutation should undergo molecular testing at the time of diagnosis, and if an EGFR mutation is identified, therapy with an EGFR TKI should be strongly considered.

The other recent randomized study regarding a genotype-directed treatment strategy was published in abstract form only thus far and is a smaller study, but all patients enrolled were positive for an EGFR mutation so the molecular results are not a subgroup analysis but the entire study cohort.[22] This trial consisted of Japanese patients with newly diagnosed advanced adenocarcinoma with EGFR mutations randomized to front-line gefitinib or front-line chemotherapy with carboplatin and paclitaxel. The primary end-point was again PFS and the study was powered for 320 patients and an anticipated HR of 0.69, favoring gefitinib. An interim analysis after 200 patients demonstrated a benefit for gefitinib with HR 0.36 (95% CI 0.25-0.51).

In sum, these studies suggest that patients harboring an EGFR mutation derive significant clinical benefit from treatment with EGFR-TKIs. As a result, EGFR TKI therapy is the emerging standard of care treatment for this population, including as front line therapy. The European Union's medicine administration recently granted approval of gefitinib specifically for patients harboring an EGFR mutation and several oncology care guidelines in the US are being modified to include EGFR mutation screening and consideration of an EGFR TKI for these patients.

2.2.2 Development of Resistance, T790M, and BIBW 2992

One clinical obstacle to EGFR TKI therapy is that all patients that benefit from TKI treatment ultimately develop drug-resistance manifesting as progression of their cancer. On average this occurs after a median of 9-12 months.[15-19, 21, 23] There is vast clinical potential in understanding the mechanisms of TKI resistance and developing strategies to reverse or prevent it.

Two main mechanisms of acquired resistance have been identified. The first is a secondary EGFR mutation, T790M, that renders gefitinib and erlotinib ineffective inhibitors of EGFR kinase activity, and the second is amplification of the MET oncogene, which activates ErbB3-dependent activation of PI3K independent of EGFR.[24-27] EGFR T790M has been detected both from tumors of EGFR mutant NSCLC patients who have developed clinical resistance to gefitinib or erlotinib and from in vitro

gefitinib-resistant EGFR mutant cell lines.[24-26, 28, 29] To date, the EGFR T790M mutation is found in roughly 50% of tumors (24 of 48) from patients that have developed acquired resistance to gefitinib or erlotinib.[26, 28, 29]

The EGFR T790M mutation occurs in an analogous position to known resistance mutations to imatinib in other kinases (T315I in ABL, T674I in PDGFRA, and T670I in KIT).[30-32] The conserved threonine residue among these different kinases, located near the kinase active site, is often referred to as the "gatekeeper" mutation. In ABL, the T315I mutation causes a steric hindrance and causes imatinib binding.[30, 33] In EGFR, the T790M mutation increases the receptor's affinity for ATP, thereby decreasing the potency of the ATP-competitive inhibitors, gefitinib and erlotinib.[34]

Cancers that become resistant to kinase inhibitors through a secondary mutation are still likely to be dependent on the activated kinase for their growth and survival. Thus, alternative strategies of inhibiting EGFR T790M may be therapeutically efficacious. This has prompted the preclinical and clinical development of second-generation irreversible EGFR inhibitors, such as BIBW 2992,which have shown activity in gefitinib-resistant preclinical models of NSCLC containing EGFR T790M.[35-37] These irreversible TKIs are able to inhibit EGFR phosphorylation and lead to growth inhibition of cell lines and xenograft models containing EGFR T790M. Irreversible EGFR inhibitors are also ATP mimetics similar to gefitinib and erlotinib, but unlike gefitinib or erlotinib, they covalently bind Cys-797 of EGFR. How the irreversible nature of these agents allows them to inhibit EGFR phosphorylation is unclear. It is possible that by covalently binding to EGFR, the local concentration of these agents near the active site increases by several orders of magnitude (compared with gefitinib or erlotinib), thus providing a means of inhibiting EGFR phosphorylation despite the presence of a T790M mutation.

While the pre-clinical evidence for activity of BIBW 2992 in NSCLC with both activating EGFR mutations and T790M is promising, it remains unknown if BIBW 2992 can overcome the T790M mutation in lung cancer patients. This study will determine if treatment with BIBW 2992 prevents the acquisition of a T790M resistance mutation

2.3 Molecular Techniques Background

2.3.1 SNaPshot Genotyping Platform

Recently, MGH implemented a multiplex molecular diagnostics platform (SNaPshot). This assay utilizes formalin-fixed paraffin-embedded tissue to quickly and economically identify 58 commonly mutated loci in 13 key oncogenes: EGFR, K-RAS, N-RAS, APC, BRAF, FLT3, JAK2, Kit, Notch, PI3K, PTEN, TP53, and beta-catenin. The DNA of interest is amplified using multiplexed PCR. Genotypes are determined using a single-base extension sequencing reaction, in which allele-specific probes interrogate loci of interest and are extended by fluorescently labeled dideoxynucleotides. The allele-specific probes have different sizes and are subsequently resolved by electrophoresis and analyzed by an automated DNA sequencer. Amplifications of EGFR, HER2, and MET and translocations in ALK are assessed using multicolor FISH assays. The SNaPshot profile has been validated and is performed in a CLIA-certified lab. It is used in place of routine EGFR and K-RAS mutation testing at our center, as it provides additional information that may be used to identify specific genetic abnormalities that correlate with tumor response to novel treatments.

Biopsies performed for this study at collaborating centers will undergo molecular analysis at MGH.

2.3.2 Circulating Tumor Cell (CTC)-Chip

The ability to metastasize is one of the hallmarks of malignancy, and though its mechanisms are not fully described, circulating tumor cell (CTC) distribution through the bloodstream appears to be a vital step in the process.[38, 39] Successful capture and characterization of CTCs has tremendous potential as a vehicle to better understand the biology of the metastatic process, and provides an avenue to explore numerous clinical applications via non-invasive, patient-specific genomic analysis. Unlike tumor-derived cells in bone marrow, which can be dormant and long-lived, CTCs have a short half-life (<1 day) and their presence indicates a recent influx from an active proliferating tumor.[40] Hence, CTCs may reflect the clinical status of cancer patients in a dynamic fashion, and could potentially be useful in the early detection of response to therapy.

At the MGH Cancer Center, investigators have developed a device called a "CTC-chip" to capture and quantify CTCs from patient blood samples. The CTC-chip is a microfluidic platform in which whole blood travels through a forest of micron-sized EpCAM antibody-coated microposts under precisely controlled laminar flow conditions. The arrangement and flow dynamics of the micropost array guides the cells gently through the chip and facilitates frequent interactions with the EpCAM antibody-coated microposts, resulting in capture of viable CTCs directly to the posts. We have demonstrated that the CTC-chip can attain successful capture of an average of 100 viable CTCs per mL of whole blood from 99% of tested advanced NSCLC patients, and that detection of EGFR mutations from isolated CTCs is feasible and correlates with tumor tissue sample testing.[41, 42] Furthermore, we showed that using an ultrasensitive allele-specific assay (the SARMS assay, by DXS) to look for EGFR mutations in the diagnostic tumor tissue samples, we identified a significant proportion of patients that had both activating EGFR mutations and low levels of detectable T790M. Though the T790M did not preclude a response to EGFR TKI therapy, it did correlate with a significantly shorter progression-free survival (7.7 months with detectable T790M compared to 16.5 months without, $p<0.001$).[42] This is consistent with other studies suggesting that T790M is present at low levels in many EGFR mutant cancers, therefore therapy with an EGFR TKI that cannot inhibit T790M allows more rapid selective growth of the resistant clone.[43]

Due to the nature of this technology (needs to be analyzed within hours of blood draw), only patients enrolled on this study at MGH will be able to submit samples for CTC analysis.

2.3.3 Interventional Radiology Repeat Biopsies

The MGH Department of Radiology provides sub-specialized care based on organ system. The Thoracic Imaging and Interventional Radiology section is directed by Dr. Jo-Anne Shepard and includes 13 providers, 6 of whom perform lung biopsies on a regular basis, totaling approximately 260 procedures per year. The thoracic service has a 4-slice multi-detector CT scanner specifically dedicated to thoracic interventional procedures. The Abdominal Imaging and Interventional Radiology section is directed by Dr. Peter Mueller and includes 20 providers, performing approximately 5000 procedures per year. The abdominal service has 3 fluoroscopic units, 2 helical CT scanners, and 2 ultrasound units specifically dedicated to abdominal intervention.

Since 2003, a total of 1719 lung/chest biopsies have been performed at MGH. Complications have included pneumothorax in 315 (18.3%), pneumothorax requiring chest tube in 43 (2.5%), and hemoptysis in 45 (2.6%). Mortality is very rare but may occur in patients with significant co-morbidities. Since 2003 lung biopsies have resulted in death for only 1 patient (0.6%). These complication rates are comparable to those reported by other major academic centers.

Over a 10-year period, 3559 liver biopsies have been performed under CT or ultrasound guidance at MGH by the GI/GU interventional radiology service; 1637 focal liver biopsies (where a focal mass was sampled) and 1922 nonfocal (where liver parenchyma was sampled for diffuse hepatic disease). Complications are categorized by the Society of Interventional Radiology criteria into three categories: 1) minor: no intervention needed or overnight admission for observation only; 2) major: requires therapy, > 48 hour hospital admission, prolonged hospitalization; or 3) death.[44] Over a 10-year period, there were 32 complications (0.9%): 13 minor (0.3%), 17 major (0.5%), and 2 deaths (0.06%). Overall, the complication rate of biopsies at MGH by interventional radiology is low.

Interventional radiology services at collaborating institutions have similar experience and safety records.

2.4 Study Rationale

As discussed above, NSCLC patients with EGFR mutations are highly likely to respond well to EGFR TK inhibition with either first-generation EGFR TKIs (erlotinib, geftinib) or with the second-generation irreversible inhibitor BIBW 2992, but resistance ultimately develops. Fifty percent of resistance to first-generation TKIs is due to the development of a secondary EGFR mutation in exon 20, the point mutationT790M. Though initially viewed as a clonal population arising in response to TKI therapy, newer research suggests that T790M is present in a small fraction of cells prior to treatment with first-generation TKIs (not detectable with standard bi-directional sequencing). Since the novel irreversible pan-HER inhibitor BIBW 2992 is highly active in lung cancers harboring activating EGFR mutations and can inhibit the EGFR T790M moiety in pre-clinical studies, a key question is whether BIBW 2992 can suppress the development of clinical resistance via T790M in lung cancer patients. The objectives of this pilot study are to estimate the effectiveness of BIBW 2992 at suppressing the development of the T790M resistance mutation in lung cancer patients. We will obtain a mandatory repeat tumor biopsy at the time of clinical progression and determine the proportion of patients that have a T790M mutation. This rate of mutation will be compared to the 50% historical data observed after development of resistance to reversible first-generation EGFR TKIs.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically or cytologically confirmed stage IIIB, IV, or recurrent non-small cell lung cancer

3.1.2 A somatic mutation in epidermal growth factor receptor (EGFR) must be present as documented by a CLIA-certified laboratory.

3.1.3 There must be radiographic measurable or evaluable disease

3.1.4 Participants must be willing, at the time of signing consent, to agree to a future biopsy of their tumor tissue at the time of disease progression, provided such a biopsy is safe and

feasible at that time. This biopsy will be subjected to genetic analyses to attempt to identify the mechanism of acquired drug resistance.

3.1.5 Performance status must be 0, 1 or 2 on the Eastern Cooperative Oncology Group scale[45]

3.1.6 Age must be ≥ 18 years

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

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- AST (SGOT)/ALT (SGPT) ≤ 3 X institutional upper limit of normal (ULN) or, if liver metastases present ≤ 5 X ULN
- Total bilirubin ≤ 1.5 X ULN
- Creatinine ≤ 1.5 X ULN or creatinine clearance ≥ 60 mL/min/1.73 m^2 for subjects with creatinine levels ≥ 1.5 x ULN .

3.1.8 The effects of BIBW 2992 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9 Participants must have the ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Prior EGFR tyrosine kinase inhibitor therapy (including gefitinib, erlotinib, or any experimental EGFR TKI agents)

3.2.2 Known brain metastases, unless they have undergone definitive therapy and are neurologically stable at the time of study entry

3.2.3 Standard chemotherapy or radiation ≤ 2 weeks of starting BIBW 2992, or experimental systemic cancer therapy ≤ 4 weeks of starting BIBW 2992. Note that prior palliative radiation to bony disease, CNS disease, or a limited thoracic area is only allowed if there is measurable or progressive disease outside the field of radiation.

3.2.4 Another malignancy within the last 3 years (except non-melanoma skin cancer or a non-invasive/*in situ* cancer)

3.2.5 Known pre-existing and clinically active interstitial lung disease

3.2.6 Significant gastrointestinal disorders with diarrhea as a major symptom (e.g. Crohn's disease, malabsorption, etc)

3.2.7 History of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia, or myocardial infarction within 6 months.

3.2.8 Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.

3.2.9 Pregnancy or breast feeding.

3.2.10 Inability to comply with the protocol

3.2.11 Participants may not be receiving any other investigational agents during the course of BIBW 2992 therapy.

3.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BIBW 2992.

3.2.13 Life expectancy < 12 weeks

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Lung cancer affects men and women, and people of all race and socioeconomic class. We do not expect the inclusion and exclusion criteria to negatively affect enrollment of underrepresented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at [redacted]

   Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the Massachusetts General Hospital Cancer Center by the Study Coordinator. See section 4.4 as for full instructions. A copy of these instructions can also be found in Appendix 3 (Multi-Center Data Safety Monitoring Plan).

Following registration, participants should begin protocol treatment within 72 hours or as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Study Coordinator should be notified of participant status changes as soon as possible.

Except in very unusual circumstances, each participating institution will order the study agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the supplier.

4.4 Registration Process for Other Participating Institutions

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Lead Institution at the following address:

- Progress note confirming performance status, lack of prior EGFR TKI, absence of CNS metastases or confirmation of the treatment and stability of known CNS metastases, absence of another malignancy within 3 years, and detailing other significant past medical history
- Copy of required laboratory, pathology, and radiology tests including:
  - Pathology report confirming NSCLC and EGFR mutation status
  - Radiology report confirming measurable or evaluable disease and cardiac ejection fraction $\geq 50\%$
  - Laboratory tests including CBC with differential, creatinine, ALT, AST, and bilirubin
  - An ECG, reviewed, signed and dated by MD listed on 1572
- Signed informed consent form. Only MDs listed on the 1572 can sign consent for the study.
- HIPAA authorization form (if separate from the informed consent document)
- Other appropriate forms (e.g., Eligibility Screening Worksheet, Registration form). The eligibility worksheet must be signed by the MD confirming the eligibility of the patient. Registrations cannot be processed without appropriate signature.

The research DF/HCC Multi-center Protocol Participating Institution will then call or e-mail the Lead Institution or designee to verify eligibility. To complete the registration process, the Lead Institution or designee will:

- Register the participant on the study with the DF/HCC Quality Assurance Office for Clinical Trials (QACT)
- Fax or e-mail the participant case number, and if applicable the dose treatment level, to the Participating Institution
- Call the research nurse or data manager at the Participating Institution and verbally confirm registration

Randomization can only occur during QACT's normal business hours of 8:00 am to 5:00 PM Eastern Time.

5. STUDY TREATMENT

5.1 Overview

This study examines first line BIBW 2992, an irreversible dual kinase inhibitor, in patients with advanced NSCLC and EGFR mutations. The primary endpoint is defining the proportion of patients with T790M on a repeat tumor tissue biopsy taken at the time of clinical progression.

5.2 Identification of the Investigational Agent

Substance (INN): BIBW 2992

Pharmaceutical form:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50 mg, 40 mg, 30 mg and 20 mg film-coated tablets (the dose of BIBW 2992 in the film-coated tablets is related to the free base equivalent of BIBW 2992)
Daily Dose:	Starting dose 40 mg with individual dose escalation to 50 mg if tolerated
Duration of use:	Continuous daily dosing until progression, unacceptable adverse events or other reason necessitating withdrawal. For administrative purposes treatment is divided into cycles which are each 4 weeks (28 days) in duration.
Route of administration:	Oral (swallowed)
Frequency:	Once daily, on an empty stomach

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than BIBW 2992 may be administered with the intent to treat the participant's malignancy while they are participating on this trial.

5.3 Administration of BIBW 2992

For administrative purposes treatment will be divided into treatment cycles, which are each 4 weeks (28 days) in duration. Patients will take a single oral dose of 40 mg BIBW 2992 each day for the first cycle (28 days).

The medication should be taken at the same time each day (± 2 hours) on an empty stomach, which is defined as at least one hour before food intake and at least three hours after food intake. The tablet should be swallowed with a glass of water. BIBW 2992 tablets are film-coated and therefore should not be chewed or crushed.

5.3.1 Missed/Vomited Dose

If a patient inadvertently does not take BIBW 2992 at their usual time, he or she may take their daily doses anytime as long as it is at least 12 hours before the next dose is due to be taken. BIBW 2992 should be taken on an empty stomach, at least one hour before food intake and at least three hours after food intake. 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.

5.3.2 Inability to Swallow Pills

BIBW 2992 should not be chewed or crushed. If patients are truly unable to swallow the tablets after an effort to conform to the protocol, the study drug may be dissolved and swallowed after dispersing the BIBW 2992 tablets according to the following procedure: Place the tablet into a glass containing 50 mL isotonic sodium chloride solution. Stir until the tablet is broken up into very fine particles (about 15 minutes). Drink the suspension immediately or administer via a gastric tube if applicable. Rinse the glass with another 50 ml of isotonic sodium chloride solution and drink or administer the supplementary solution via the gastric-tube again (to pick up any drug remaining in the glass/gastric-tube). Isotonic sodium chloride must be prescribed by the investigator if this protocol is to be used, and prospective patient-specific permission to use the dissolving protocol must be obtained from the local IRB.

5.4 Individual Patient Dose Escalation to 50 mg

During the first cycle of therapy at 40 mg daily, if the patient experiences ≥ Grade 1 diarrhea, skin-related adverse events or mucositis or any drug-related event ≥ Grade 2, the dose of BIBW 2992 should be continued at 40 mg (unless dose reduction is necessary - see section 5.5). For a description of CTCAE grading of toxicities, see Appendix 2.

If none of the above events are experienced during the first cycle of treatment, the dose for Cycle 2 should be increased to 50 mg each day. The patient should remain on 50 mg for subsequent treatment cycles, unless dose reduction is necessary (see section 5.5).

Dose escalation is prohibited in any situation other than that described above.

5.5 Dose Modification

In the event of mild (grade 1 or transient grade 2) treatment-related toxicities, BIBW 2992 may be held for up to 14 days and then restarted at the same dose at the investigator's discretion. If toxicity is more severe, meeting the criteria outlined below, the treatment with BIBW 2992 should be handled according to the schedule in Table 2.

Table 2. Dose Reduction Scheme

AE type and grade	Action	Dose reduction scheme
Events related to study drug;		
• Any **drug related** AE CTCAE Grade ≥3.	Hold treatment with BIBW 2992 until patient has recovered to CTCAE Grade ≤ 1 or baseline[1] . Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to CTCAE Grade ≤ 1 or baseline[1] within 28 days study treatment should be permanently discontinued[2] .	If patient was receiving 50 mg, resume treatment at a dose of 40 mg.
• CTCAE Grade ≥2 diarrhea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrheal medication/hydration.		If patient was receiving 40 mg, resume treatment at a dose of 30 mg.
• CTCAE Grade ≥2 nausea and/or vomiting persisting for 7 or more consecutive days despite anti-emetic treatment/ hydration.		If patient was receiving 30 mg, resume treatment at a dose of 20 mg.
• CTCAE Grade ≥2 worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50% from baseline.		If patient was receiving 20 mg, discontinue BIBW 2992.

1 Baseline is defined as the CTCAE grade at the start of treatment
2 In the event that the patient is deriving obvious clinical benefit in the opinion of the investigator, but has not recovered within 28 days of holding drug, the further treatment of the patient may occur only after consultation with the principal investigator and obtaining permission for protocol deviation from the IRB.

Important notes regarding dose reduction:

- If the patient meets one of the AE criteria outlined in the left column of table 2, dose reduction must occur after holding the drug and allowing toxicities to resolve to CTCAE grade 1 or baseline.

- In addition, patients must discontinue treatment if they experience deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥3.

- In the event of a prolonged (≥7 consecutive days) Grade 2 drug-related event not listed in table 2, which is poorly tolerated by the patient, the investigator may choose to hold BIBW 2992 for up to 28 days to allow the patient to recover, followed by a dose reduction according to the schedule in table 2.

- In the event of an adverse event that is not related to treatment or a serious adverse event that is not related to treatment, or another reason at the investigator's discretion, the investigator may choose to pause the medication for up to 7 days to allow the patient to recover. No mandatory dose reduction need occur in this case.

5.6 Compliance and Accountability

A drug diary will be provided to each patient that corresponds to each cycle of therapy. Completed drug diaries will be collected on a regular basis, compared with returned pill counts, and evaluated for compliance. At the end of the study, unused supplies of BIBW 2992 should be destroyed according to institutional policies.

5.7 Packaging, Labeling, Re-supply, and Storage

BIBW 2992 will be supplied as film-coated tablets. Available dosage strengths will be 20 mg, 30 mg, 40 mg and 50 mg. Tablets will be supplied in HDPE, child-resistant, tamper-evident bottles. Bottles will be labeled according to local regulations and will include the following as a minimum:
• Study number
• Product name (e.g., BIBW 2992)
• Contents of the bottle (e.g., 30 tablets)
• Tablet strength
• Batch number
• Use-by date
• Storage information
• Instructions for use
• Sponsor name and address
• A statement that the medication is for clinical trial use only
• A caution statement

A new bottle of medication will be dispensed on day 1 of each cycle, regardless of the number of tablets remaining in the bottle from the previous cycle. The patient will initially receive one bottle of 40 mg tablets and in the event that dose increase or reduction is necessary the patient will return to the clinic and new medication will be dispensed.

BIBW 2992 must be stored in the original packaging. Film-coated tablets are humidity sensitive and therefore bottles must be kept tightly closed. Tablets will be stored at the study site in a limited access area and must not be stored above 25ºC.

5.8 Pre-treatment Criteria

5.8.1 Cycle 1, Day 1

Patients will be eligible for treatment with BIBW 2992 at the start of protocol therapy if they meet all study eligibility criteria.

5.8.2 Subsequent Cycles

Patients will be eligible for retreatment with BIBW 2992 every 28 days, provided that any treatment-related toxicities requiring treatment delay (see Section 5.5) have resolved to ≤ grade 1 or baseline within 28 days. If retreatment criteria are not met within this period, the subject must be withdrawn from the study.

Patients may continue on study treatment indefinitely, in the absence of meeting one of the criteria for discontinuation from study treatment (see Section 5.10).

5.9 General Concomitant Medication and Supportive Care Guidelines

Patients should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate) or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit.

Other supportive medications may be used as per institutional guidelines.

5.9.1 Suggested Management of Diarrhea

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with BIBW 2992. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide (Imodium) controls diarrhea caused by BIBW 2992.

The recommendations for management are as follows:

- If any diarrhea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets (total dose 4 mg) should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 8 tablets (16 mg).

- Other anti-diarrheal medications that could be used include: Lomotil (5 mg, four times a day), or tincture of opium (15-20 drops orally every 4 hours) or octreotide (150 to 300 µg SQ twice a day).

- Oral hydration is important regardless of severity of diarrhea; appropriate rehydration (1.5 L/m2/day plus equivalent of actual fluid loss) and electrolyte replacement should be recommended in the event of CTCAE Grade 2 and Grade 3 diarrhea.

- For CTCAE Grade 3 diarrhea or CTCAE Grade 2 diarrhea lasting ≥ 2 days (48 hours) despite adequate antidiarrheal treatment, BIBW 2992 must be held until recovery to CTCAE ≤ Grade 1. Upon recovery, BIBW 2992 should be resumed at a reduced dose according to the dose reduction scheme outlined in Section 5.5

- If despite optimal supportive care and a treatment pause, diarrhea does not resolve to CTC Grade ≤1 within 28 days, the patient should be removed from protocol therapy.

5.9.2 Suggested Management of Rash

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and reduce the rash. The recommendations for management are as follows:

- **General/Prevention**: strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream.

- **CTCAE Grade 1 rash***:* mild rash may not need treatment. However, if treatment is considered necessary, moisturizing lotions, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.

- **CTCAE Grade 2 rash**: relief from major symptoms caused by CTCAE Grade 2 skin-related adverse events should be achieved by a combination of local and systemic therapies including:

  1) Systemic antibiotics (doxycycline or minocycline etc.).
  2) Topical treatment (hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream).

  And / or

  1) Antihistamines (diphenhydramine, etc.)
  2) Oral prednisone (short term i.e., <14 days treatment) may be added at investigator's discretion.

  Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continue until improvement or resolution to CTCAE Grade ≤1. As above, treatment may be held for up to 7 days and restarted at the same dose at the discretion of the investigator. If grade 2 rash persists for ≥ 7 days despite treatment and is poorly tolerated by the patient, treatment should be held for up to 28 days followed by a reduction in the dose of BIBW 2992 according to the dose reduction scheme in Table 2, see Section 5.5.

- **CTCAE Grade 3 (or greater) rash:** may be treated in a manner similar to CTCAE Grade 2 rash. In the event of CTCAE Grade ≥3 rash, treatment with BIBW 2992 should be held until recovery to CTCAE Grade ≤1. Treatment should be resumed at a reduced dose (see Section 5.5). If CTCAE Grade ≥3 rash does not resolve to CTCAE Grade ≤1 within 28 days of stopping BIBW 2992 treatment and despite optimal supportive care, the patient should be removed from study.

5.9.3 Suggested Management of Interstitial Lung Disease

Although quite rare, interstitial lung disease (ILD) is a class effect of EGFR TKIs and can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. Chest CT should be obtained to look for interstitial fibrotic changes if ILD is suspected. In the event that ILD is suspected, drug treatment should be discontinued and the patient should receive appropriate medical management and supportive care. Although there is no established treatment, systemic corticosteroids are often administered. BIBW 2992 should not be restarted in those patients suspected of having drug-related ILD and the subject should be removed from the study.

5.10 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may be given continuously until one of the following criteria applies:

- Disease progression by RECIST criteria (see Section 8.3) Note that if a patient has progression by RECIST but is still deriving clinical benefit and there is not likely to be harm from continuing treatment, patients may continue therapy until no longer clinically benefitting, after discussion with and approval by the Sponsor, Dr. Sequist.
- Retreatment criteria are not met within the specified time frame (see Section 5.5)
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- Death
- Lost to follow-up

5.11 Duration of Follow Up

Participants will be followed for survival after removal from study until death. Participants removed from study for unacceptable adverse events will be followed for safety until resolution or stabilization of the adverse event.

6. SAFETY ASSESSMENTS AND ADVERSE EVENTS

6.1 Overview

Safety measurements that will be used in the study include physical examinations, periodic eye examinations, and clinical laboratory tests (hematology, blood chemistries, creatinine and liver function tests). Toxicities will be defined and graded using Version4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The adverse events expected with BIBW 2992 are summarized in Section 2.1 of the protocol and are cataloged thoroughly in the Listed Adverse Events section of the Investigator's Brochure, which is on file with the Principal Investigator.

If possible, symptoms from adverse events should be managed aggressively with supportive care. See Section 5.9 for specific recommendations about managing rash, diarrhea and interstitial lung disease.

All adverse events experienced by participants will be collected from the time of signing informed consent, through the period of treatment, until the final study visit and repeat tumor tissue biopsy occur (see Section 9). Participants continuing to experience toxicity at the post-biopsy off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1.2 History and Physical Examination

The relevant interval history should be obtained during screening and at the start of each cycle. Interval histories should include elicitation of interim illnesses and adverse events. If a subject remains on study treatment for more than 8 cycles, these assessments may occur every other month, see Section 9.

A problem-focused physical examination (PE) will be performed during screening, at the start of each cycle, on days 8 and 15 of cycle 1, and at the time of study discontinuation. If a subject remains on study treatment for more than 8 cycles, these assessments may occur every other month, see Section 9. Every PE should include measurement of body weight, vital signs, and evaluation of the ECOG performance score (see Appendix 1). Blood pressure must be recorded at each visit. Measurement of height need only occur at the screening PE.

6.1.3 Laboratory Examinations

Laboratory examinations to be performed during screening include hemoglobin, white blood cell count including neutrophil count (sum of polysegmented granulocytes and band forms), platelets, bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium, electrolytes (sodium, potassium), and a urine pregnancy test (for women of child-bearing age).

Laboratory examinations are to be performed at the start of each cycle of treatment, on days 8 and 15 of cycle 1, and at the time of study discontinuation include hemoglobin, white blood cell count including neutrophil count (sum of polysegmented granulocytes and band forms), platelets, bilirubin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, calcium and electrolytes (sodium, potassium).

6.2 Definition of Terms

6.2.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after signing informed consent or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

6.2.2 Serious adverse event (SAE)

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 sever 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

6.2.3 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

6.2.4 Unexpected adverse event

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.

6.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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.

6.3 Procedures for AE and SAE Recording and Reporting

Reporting or participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. Each recorded AE or SAE will be described by its duration (i.e., start and end dates), intensity treatment required, grade, suspected relationship to the investigational product (causality), outcome and actions taken with investigational product.

The descriptions and grading scales found in the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. The CTCAE version 4.0 is located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **YES**

  There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge.

- **NO**

  Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug).

Each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator. Specific reporting requirements are detailed below.

6.3.1 Serious Adverse Event Reporting

6.3.1.1 Reporting to the Institutional Review Board

All serious adverse events that occur, during treatment, or within 28 days of the last dose of treatment must be reported to the DFCI Office for Human Research Studies (OHRS). Events that occur after consent but before study enrollment/registration and receiving study treatment do not need to be reported. This includes events meeting the criteria outlined in Section 6.2.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 28 days of the last study intervention.

  Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.
Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

6.3.1.2 Reporting to Boehringer Ingelheim (BI)

All AEs reported as an expedited Safety Report to the FDA, all other Serious adverse events and Non-serious AEs occurring at the same time and/or which are medically related to the SAE must also be reported to Boehringer Ingelheim using the BI SAE form per the timelines indicated in the Pharmacovigilance Agreement.

6.3.1.3 Reporting to Hospital Risk Management

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

6.3.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported on the toxicity Case Report Forms.

6.4 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from signing of the informed consent, throughout the study, and within 28 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should report any serious post-study event(s) that might reasonably be related to participation in this study, including any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

6.5 Contraception and Pregnancy

Female patients who are not of childbearing potential due to being postmenopausal (2 years without menses) or surgical sterilization (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception. All other female patients are considered to have childbearing potential and should use adequate contraception throughout the study (from screening until end of study participation or 28 days after last dose of trial medication, whichever is later).

Acceptable methods of contraception for females include hormonal contraception and double barrier method. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and IUD (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). If hormonal contraceptives are used, at least one barrier method should also be used. Partner vasectomy, natural 'rhythm' and spermicidal jelly/cream are not acceptable as methods of contraception.

Male patients should use adequate contraception throughout the study (e.g. condom and spermicidal jelly).

Female patients must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing study treatment. If a patient is found to be pregnant during study participation, this should be handled as follows:

Timing of Pregnancy	**Action**
Prior to starting study medication	Patient should be withdrawn from the study immediately. No reporting necessary.
During study treatment	Treatment must be stopped immediately and the pregnancy should be reported immediately using the pregnancy form. If the investigator wishes to give any further treatment with study medication, this must be discussed and agreed with Boehringer Ingelheim. The pregnancy should be followed up to final outcome including any premature termination. Only reports of premature termination should be reported to the Boehringer Ingelheim on the BI SAE form. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine fetal demise/death) must be reported as an SAE.
During follow-up (after finishing treatment but before end of study participation), or within 28 days of last dose of study medication (even if no longer participating in study)	The pregnancy should be captured using the pregnancy form. The pregnancy should be followed up to final outcome including any premature termination. Only reports of premature termination should be reported to Boehringer Ingelheim on the BI SAE form. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine fetal demise/death) must be reported as an SAE.

7. MOLECULAR AND CORRELATIVE STUDIES

7.1 Repeat Biopsies for Molecular Testing

It is expected that all patients will undergo a repeat tumor tissue biopsy at the time of removal from study treatment. Ideally, the lesion to be biopsied should be new or growing on BIBW 2992 therapy. The purpose of this biopsy is to assess for the presence or absence of the resistance mutation T790M. This is the primary end-point of the study. In most cases, the repeat biopsy will be at the time of clinical progression. If a patient is being removed from treatment for reasons other than clinical progression (e.g. withdrawal of consent, intolerance of side effects, etc) then a repeat biopsy is desirable but not required.

7.1.1 Requirements for Repeat Biopsy

- For Thoracic IR Biopsies: Each patient must be assessed for risk and approved by thoracic interventional radiology as having a candidate lesion that measures at least 8 mm on a chest CT scan and is appropriate for percutaneous bipsy. Risk assessment includes an evaluation of the extent of emphysema and pulmonary fibrosis, risk of procedure-related pneumothorax as estimated by the location of the lesion and the presence of bullous disease in the targeted path of the biopsy needle, and CT evidence of pulmonary arterial hypertension or significant cardiac disease. Lung biopsies will not be performed in patients with chronic lung disease requiring supplemental oxygen at home or in patients with known moderate or severe pulmonary arterial hypertension, valvular disease or cardiomyopathy.

- For Abdominal IR Biopsies: Each patient must be assessed for risk and approved by GI/GU interventional radiology as having a candidate lesion that is appropriate for percutaneous biopsy. Risk assessment includes an evaluation of the risk of bleeding and risk of perforation of visceral structures given the location of the target lesion.

- No aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), or other anti-platelet medication is allowed for 7 days prior to biopsy.

- No low molecular weight heparin is allowed for 12 hours prior to biopsy.

- Prothrombin time must be < 14 seconds, assessed within 2 weeks of biopsy or within 72 hours of biopsy if on chronic warfarin or other anti-coagulation therapy.

- Platelet count must be > 75,000, assessed within 2 weeks of biopsy

- Patients who have a bony metastatic site as the planned site for repeat biopsy, unless there is a significant soft tissue component that can be sampled, as the decalcifying material used to process osseous biopsies denatures DNA and the material is therefore not suitable for molecular analysis.

- Significant co-morbidity or orthopedic condition that may impede optimal positioning during biopsy and/or post-biopsy recovery

- Patients must have an adequate family/caregiver support system to ensure sufficient observation after the outpatient biopsy. If patient dose not have a support system, arrangements will be made for overnight admission after the biopsy to observe for potential complications.

7.1.2 Procedure for Repeat Biopsy

Once the case is approved by interventional radiology for its appropriateness for biopsy the biopsy will be scheduled and performed in the usual manner. The lesion will be identified by either ultrasound or CT imaging. The interventional radiologist will select a safe path to the lesion. An intravenous cannula will be placed and sedation will be administered as per routine clinical protocol. Typical sedation medications include a combination of intravenous midazolam and fentanyl. Subcutaneous lidocaine will be administered and then a 17-19 gauge metal cannula will be inserted percutaneously into the lesion with visual confirmation by either CT or ultrasound. The interventional radiologist will attempt to obtain two or more 1-2 cm long 18-20-gauge core biopsy samples and three ore more 22 gauge fine needle aspirates of tissue using a cutting core biopsy needle or 22 gauge needle. The normal departmental pre-procedural documentation, procedure note documentation and post-procedure observation and discharge algorithms will be performed as per standard practice. Note: biopsies may be obtained at the location of collaborating investigators, i.e. patients are not required to travel to MGH for their biopsies. These centers should follow the procedures as outlined in the protocol or call Dr. Sequist at MGH to discuss any major variations in biopsy practice from the protocol document.

7.1.3 Molecular Assessment of Repeat Biopsy Tissue

Repeat biopsy tumor tissue will be handled under the following procedures. One slide will be routed to anatomic pathology, to confirm that the lesion biopsied is malignant and appears as expected from a histologic standpoint given the presumptive diagnosis. The majority of the sample will undergo genotyping analysis with the SNaPshot platform as described in Section 2.3.1. Note: if the biopsy is taken at another hospital besides Massachusetts General Hospital, anatomic confirmation of the diagnosis should still occur at the hospital performing the biopsy (using as little material as possible). The rest of the material will be formalin-fixed and paraffin-embedded, and should be routed to Dr. Sequist at MGH for analysis with the SNaPshot platform. Samples should be shipped with a requisition form (see Appendix 4) to:

[redacted]

The primary use of the material obtained from repeat biopsies will be to assess T790M status from resistant specimens. We will also determine if there is MET amplification, another validated mechanism of acquired resistance. However, when there is sufficient tissue, we will perform other exploratory genomic, proteomic and expression profiling and attempt to develop patient-specific tumor models *in vitro* and *in vivo*. The establishment of such models will allow us to functionally validate or refute the hypothesized mechanisms of resistance to BIBW 2992. We have had success with these techniques in the past and will perform these studies in collaboration with Dr. Bo Rueda who has an established track record of developing xenograft tumor models and cell lines from patient specimens. Leftover material will be returned to the participating institution at the completion of the study.

7.1.4 Follow-Up after Repeat Biopsy

All subjects will be seen in clinic for follow-up and assessment of biopsy-related complications at 7 days post-biopsy (±2 days) and again at ≥ 30 days post-biopsy.

7.2 Circulating Tumor Cell Studies

Blood samples for CTC analysis will be collected at the following time points.

- Day 1, prior to therapy
- Day 1, three hours after dose
- Day 8
- Day 15
- Cycle 2, day 1
- Cycle 3, day 1
- Cycle 4, day 1
- Cycle 5, day 1
- Then every 2 cycles
- At the time of progression (end of study visit)

CTCs will be assessed from each peripheral blood using the CTC-Chip (see Section 2.3.2). This assay will be performed under the supervision of Dr. Daniel Haber. Blood samples will be same-day couriered to the Haber Lab in the Charlestown Navy Yard at MGH. Blood samples will be stored on a rocking platform to prevent cell settling and will be processed within 24 hours of blood draw. Whole blood will be passed through the CTC-chip using standard procedures as previously published[41]. Captured CTCs will be fixed on the CTC-chip and stained to identify DNA content, epithelial cells and nonspecifically bound leukocytes. Cells staining positive for nuclear content and positive for cytokeratin will be counted as CTCs. The number of CTCs per milliliter of blood will be determined by comprehensive image analysis, scanning the entire chip and identifying CTCs based on cell size, morphology and fluorescence staining. The association of CTC numbers with radiographic disease response and recurrence will be assessed.

Captured CTCs will then be lysed and DNA content will be collected. Allele-specific sensitive methods will be used to determine the T790M status of the captured cells, as previously published.[42] If sufficient material is available, exploratory analyses will also be performed such as whole genome amplification of DNA and analysis with the SNaPshot platform. CTC-based genotypes will then be correlated with tumor-derived genotypes.

8. EFFICACY ASSESSMENT

Although response is not the primary endpoint of this trial, participants with measurable and/or non-measurable disease will be assessed by RECIST version 1.1 criteria. For the purposes of this study, participants should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks following initial documentation of an objective response.

Response and progression will be evaluated in this study using the criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST)guideline.[46] Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

8.1 Definition of Terms

8.1.1 Evaluable Cohorts

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective 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 response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

8.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

Reminder: *A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.*

Non-measurable disease.

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

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. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated

areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions.

All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

8.1.3:**Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or 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 when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For 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. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

8.2 Response Criteria

8.2.1 Evaluation of Target Lesions

Complete Response (CR):

Disappearance of all target lesions. Any pathological lymph node 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 with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

***Definition of New Lesion**: 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 (ex: new bone lesions may be 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.

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.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

8.2.2 Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions. Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: 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 (ex: new bone lesions may be healing or flare of pre-existing lesions). 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.

8.2.3 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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 3. Evaluation of Best Overall Response For Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response for 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	

* 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.

Table 4. Evaluation of Best Overall Response For Patients with Non-Measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

Non-CR/non-PD	No	NonCR/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 an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

8.3 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 recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

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 recurrent disease is objectively documented.

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.

8.4 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression or death

8.5 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to death.

9. STUDY CALENDAR

Screening evaluations are to be conducted within 4 weeks prior to start of protocol therapy, unless otherwise noted. All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Screening	**Treatment Period (± 3 days)**										**Off-Study[a]**	**Survival Follow-up**
Cycle[b] (C) and Day (D)	Day-28 to 0	C1 D1	C1 D8	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8+		
Informed consent and confirmation of eligibility	X												
Medical History, Vitals, Physical Exam and AEs[c]	X	X	X	X	X	X	X	X	X	X	X[d]	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X[d]	X	
Laboratory testing[e]	X	X	X	X	X	X	X	X	X	X	X[d]	X	
ECG	X												
Tumor assessment (RECIST)[g]	X					X		X		X	X[g]	X	
Circulating Tumor Cell (CTC) Assay[h]		X	X	X	X	X	X	X		X	X[h]	X	
Repeat Tumor Biopsy[i]												X	X[i]
Survival and subsequent therapy[j]													X

a **Off-Study visit** – The off-study assessments will be performed when the subject meets criteria for study discontinuation (see Section 5.10).

b **Cycles** are 28 days long

c **Vitals** include temperature, blood pressure, respiratory rate, pulse, height, weight, performance status. **Medical history** should include recording all interim illnesses and assessment of **adverse events**.

d **After Completion of Cycle 8** visits for medical history, vitals, physical exam, assessment of adverse events, concomitant medications and laboratory evaluations need only be done every 2 months. These visits will correspond with the schedule for restaging scans (see below) and can be thought of as occurring after cycles 8, 10, 12, etc or can also be thought of as occurring at the beginning of cycles 9, 11, 13, etc.

test (if applicable). Studies to be done at the start of each cycle of treatment include CBC, LFTs, BUN, Cr, calcium, and electrolytes.

f **f Tumor Measurement** – Baseline scans can be performed up to 28 days prior to start of treatment. Follow-up scans should be performed within 10 days of the start of cycles 3, 5, 7, 9, etc. This can also be thought of as following cycles 2, 4, 6, 8, etc.

g **Circulating Tumor Cell Assay** – Samples for CTC analysis will be drawn Day 1 prior to therapy, Day 1 three hours after dose, Day 8, Day 15, Cycle 2 day 1, Cycle 3 day 1, Cycle 4 day 1, Cycle 5 day 1, then every 2 cycles, and at end of study visit, see Section 7.2
CTC collection at MGH only.

h **Assessment of Requirements for Repeat Biopsy** – To be performed at the time of progression, see Section 7.1.1. Includes interventional radiology review of films for biopsy, holding of anti-platelet and anti-coagulation medications, assessment of PT, PLTs. **Repeat biopsy** should be performed as in Section 7.1 and submitted for molecular analysis and the patient should be seen for a follow-up visit to assess post-biopsy complications at 7 days (± 2 days) and at ≥ 30 days post-biopsy

i **Survival follow-up** - After discontinuation from the study for any reason, where possible the patient, patient's family, or the patient's current physician must be contacted every 12 weeks for survival information until death. All subsequent chemotherapy, radiation, surgical or other anti-cancer therapies are to be collected until death. A statement of death form should be submitted at any point during the study when a patient has died. In addition, any patient who discontinued study treatment for reasons other than objective disease progression should continue, where possible, to have objective tumor assessments every 8-12 weeks in order to collect information on progression of disease.

10. DATA AND SAFETY MONITORING

10.1 Data Reporting

10.1.1 Method

The QACT will collect, manage, and monitor data for this study.

10.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

10.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. 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 Principal Investigator and study team.

The DSMC will meet quarterly and/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 within 30 days for Phase I or II protocols; for gene transfer 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.

10.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

11. REGULATORY CONSIDERATIONS

11.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

11.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

11.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

11.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a pilot study examining the feasibility of using acquisition of a resistance mutation as the primary endpoint for a clinical trial. NSCLC patients with EGFR mutations are highly likely to respond well to EGFR TK inhibition with either first-generation EGFR TKIs (erlotinib, geftinib) or with the second-generation irreversible inhibitor BIBW 2992, but resistance ultimately develops, see Background. Current literature consistently estimates that fifty percent of resistance to first-generation TKIs is due to the development of a secondary EGFR mutation in exon 20, the point mutationT790M. Since the novel irreversible pan-HER inhibitor BIBW 2992 is highly active in lung cancers harboring activating EGFR mutations and can inhibit the EGFR T790M moiety in pre-clinical studies, a key question is whether BIBW 2992 can suppress the development of clinical resistance via T790M in lung cancer patients.

The study will consist of 24 TKI-naïve patients with mutations in EGFR. Given our relatively large population of referral patients at DF/HCC with EGFR mutations and the collaboration with a few select other centers, This sample size was felt to be feasible to enroll within a three year time period. Each subject will be expected to remain on therapy for approximately 10 months. Therefore within 3.5 years it is expected that we will complete at least 16 of the progression biopsies.

All patients will initially be treated with BIBW 2992 at 40 mg daily, though as in other studies with this compound, dose escalation to 50 mg will be permitted for individual patients after one cycle if there are minimal adverse events at 40 mg. Tumor tissue biopsy for comprehensive genomic profiling is mandatory at the time of acquired resistance (clinical progression). The primary endpoint will be to determine the proportion of patients with T790M resistance mutations at the time of progression. The data collected will be vital in determining the optimal strategy for future studies comparing the efficacy of BIBW 2992 to first-generation EGFR TKIs.

The primary objective is:

1. To determine the proportion of patients that have a T790M mutation on their progression biopsy and to compare this with published data for first-generation EGFR tyrosine kinase inhibitors

The secondary objectives are:

1. To estimate the response rate
2. To estimate the progression-free and overall survival
3. To describe the safety of obtaining repeat tumor biopsies for genotype analysis
4. To describe other mechanisms of resistance (besides T790M) observed on the progression biopsies

5. To explore the results of experimental CTC-derived genotype assessed from serial blood samples taken during therapy with BIBW 2992 and to compare CTC-derived results with those from the progression biopsies

12.2 Sample Size/Power Calculation for the Primary Endpoint

Based on prior data the rate of T790M at the time of progression on first-generation EGFR TKIs (gefitnib/erlotinib) is 50%.[26, 28, 29]

The null hypothesis is that BIBW 2992 therapy yields the same rate of T790M at the time of progression (50%).

It is expected that approximately 6 of the patients will not undergo a repeat biopsy, despite consenting to the biopsy at the time of enrollment. Reasons for not having a biopsy may include patient withdrawal of consent or not having a lesion that is safe and feasible to biopsy at the time of progression. Therefore, power calculations were performed assuming there would be 18 biopsies performed.

With 18 biopsies and a significance level of 0.05, and using a one-sided binomial test, we can achieve 86% power to detect the alternative hypothesis that BIBW 2992 therapy yields a 20% rate of T790M at the time of progression. The alternate hypothesis implies that BIBW 2992 may be better at suppressing T790M as a mechanism of acquired drug resistance.

12.3 Data to Be Analyzed

Evaluable for the primary endpoint (acquisition of T790M): All patients who undergo a repeat biopsy will be evaluable for acquisition of T790M. If the results of this test are not interpretable due to technical failure of the assay, T790M will be assumed to be present (the more conservative assumption in terms of affecting the primary endpoint). Patients that do not undergo a repeat biopsy will not be included in the primary endpoint analysis.

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective 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 response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

12.4 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

12.5 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

12.6 Safety of Treatment

A summary of the adverse events and their attributed relatedness to treatment will be provided.

12.7 Analysis of Response Rate

Response rate will be assessed as per RECIST, see Section 8.3. Results will be reported with 95% confidence intervals.

12.8 Analysis of Progression-Free and Overall Survival

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.

12.9 Analysis of Repeat Biopsy Complications and Results

Complications arising from repeat tumor biopsies for genetic analyses will be recorded at the two post-biopsy required visits or at any other time that they become apparent and will be reported annually to the IRB as part of the continuing review application (unless they meet SAE reporting criteria, in which case they will be reported immediately). At the end of the study, the complications will be summarized and presented together with the rest of the study data in a descriptive fashion.

Other molecular findings from the tumor repeat biopsies at the time of clinical progression will be presented in a descriptive format.

12.10 Analysis of Circulating Tumor Cells

CTC samples will be used in exploratory analyses, see Section 7.2. Results of CTC studies will be presented in a descriptive fashion and will be hypothesis-generating only.

13. PUBLICATION PLAN

At the end of the study, the results will be analyzed and a manuscript submitted for peer review within 24 months of the end of data collection. As this is a pilot study, there is no other pre-specified plan for the timing of public release of data.

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15. APPENDICES

Appendix 1: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 2: CTC Grading Information

The descriptions and grading scales found in the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. The CTCAE version 4.0 is located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

A link to this website will be included as part of the electronic oncology protocol system at DF/HCC.

Appendix 3: Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan for Protocol # 10-092

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations; Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CHB, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.). The Lead Institution is the home of the Overall PI.

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A Participating Institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The Participating Institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the

Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

Clinical Trials Office: The clinical trials offices of the DF/HCC consortium members support investigators and their study teams with the coordination, submission and ongoing conduct of research protocols involving human subjects. Specifically, these offices support four core service areas including; pre-review of PI initiated protocols; assistance in the preparation and management of Investigational New Drug (IND) applications and subsequent required reporting to the FDA; regulatory consultation and guidance in the interpretation of local, federal, and ICH/GCP guidelines and policies; and the orientation and ongoing training support of clinical research personnel.

DF/HCC Quality Assurance Office for Clinical Trials: The DF/HCC QACT is a unit that has been developed to computerize, manage, and QC & QA data and DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to audit DF/HCC trials.

2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair, Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Dr. Lecia Sequist will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling subjects.
- For international trials, assure that the protocol is provided to Participating Institutions in the primary language spoken at the site.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Communicate regularly with each Site Investigator
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.

- Act as the single liaison with FDA for this investigator-held IND trial

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution, Massachusetts General Hospital Cancer Center, will ensure that all Participating Institutions within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and HIPAA requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of FWA and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain FDA correspondence
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute Serious Adverse Event safety reports (both IND Safety reports and protocol specific SAEs).
- Monitor at Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Verify that eligibility has been confirmed by the investigator and that appropriate consent has been obtained.
- Provide auditing services (funding and QACT approval required).

2.3 Participating Institution

Each Participating Institution will provide to the Coordinating Center a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.

The general responsibilities for each Participating Institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event reports to local IRB and directly to the Coordinating Center.
- Submit deviations and violations to local IRB and the Coordinating Center.
- Secure investigational agents per federal guidelines and protocol requirements.
- For protocols using investigational agents, the Participating Institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company)

3.0 PROTOCOL DEVELOPMENT

3.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and FDA Guidelines. Further, the Protocol Chair will be the single liaison with FDA.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify, qualify and initiate Participating Institutions and obtain accrual commitments.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

3.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Maintain Regulatory documents for all Participating Institutions.
- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all Participating Institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Conduct regular communications with all Participating Institutions (conference call, emails, etc)
- Maintain documentation of all communications.

4.0 PROTOCOL MANAGEMENT

The Coordinating Center is responsible for assuring that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Coordinating Center must maintain copies of all IRB approvals, for each Participating Institution.

4.1 Protocol Distribution

The Coordinating Center will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

4.2 Protocol Revisions and Closures

The Participating Institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating Institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval

Protocol Closures and Temporary Holds: Participating Institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

4.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent from participating institutions. As best a possible, the template should be followed with the specifications outlined in the DF/HCC guidance document on Model Consent Language.

Participating sites are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Lead Site for their revision prior to submission to the participating site's IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. **It is DF/HCC policy that only attending physicians can obtain informed consent and re-consent to drug and/or device trials.**

4.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee and must be submitted and approved by the DFCI IRB prior to participant registration:

- Approval Letter of the institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution's IRB
- IRB approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the DF/HCC Lead Institution their IRB approval for Amendments to a protocol.

4.5 IRB Re-Approval

Annual IRB re-approval from the Participating Institution is required in order to continue research and register participants onto a protocol. There is no grace period for continuing approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution from the Participating Institutions on or before the anniversary of the previous approval date.

4.6 Participant Confidentiality and Authorization Statement

The HIPPA of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol, the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol Participating Institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

4.7 Participant Registration and Randomization

To register a participant, please refer to page 18, section 4.4 for details regarding the registration process.

4.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

4.9 DF/HCC Multi-center Protocol Registration Policy

4.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy.

4.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without prior DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

4.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

4.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

4.10 Schedule of Data Submission

The DF/HCC QACT develops a set of either paper or electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. QACT provides a web based training for eCRF users. These forms are designed to collect data for each study. *Note: It is necessary to send only ONE copy of all paper Case Report Forms, if applicable.*

4.10.1 Eligibility Checklist

Purpose - Outlines protocol-specific eligibility criteria and includes the following:

Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)

1) Parameters for eligibility
2) Parameters for exclusion

4.10.2 On-study Form(s)

Purpose - documents the following items:

- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant's physical status at protocol registration
- Disease site specific data

4.10.3 Baseline Assessment Form(s)

Purpose – Documents objective and subjective disease status as defined by the protocol**.** Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

4.10.4 Treatment Form(s)

Purpose - Records the following information related to the time the participant receives protocol treatment:

- Participant, Protocol information
- Protocol treatment and supportive therapy per treatment cycle
- Protocol specific laboratory values per treatment cycle
- All medications other than protocol chemotherapy agents used to treat concomitant diagnoses, if applicable

4.10.5 Adverse Event Report Form(s)

Purpose – Documents adverse events that occur while the participant is receiving treatment and for up to 30 days after the last dose of treatment. All adverse events are to be graded by number using the toxicity grading scale required by the protocol. *This form is not for IRB submission, but for recording the AE in the research database.*

4.10.6 Response Assessment Form(s)

Purpose – Documents objective and subjective response as defined by the protocol. Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

4.10.7 Off Treatment and Off Study Form(s)

Purpose - The Off Treatment and Off Study Forms are submitted when the participant is removed from the study or has completed all protocol treatment. Note: If the participant dies while on protocol**,** the Off Study Form is the last form submitted.

4.10.8 Follow up / Survival Form

Purpose - Summarizes participant status at a given point in time after being removed from treatment.

4.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Completeness:
Is all the information provided as required per protocol?

Protocol Treatment Compliance:
Are the drug dosage and schedule correct?

Adverse Events (Toxicities):
Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

4.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

5.0 REQUISITIONING INVESTIGATIONAL DRUG

Participating Institutions should order their own agent from Boehringer Ingelheim Pharmarceuticals, Inc.'s contracted distributor for this trial, Almac. The Almac Supplies Order Form and complete instructions will be given to each site in the start-up materials.

6.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

6.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

6.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs):

Sites within DF/HCC will report serious adverse events meeting the reporting criteria directly to the Office for Human Research Studies, BI and the FDA. Other participating institutions should report events that meet the reporting criteria by forwarding the complete institutional SAE forms to:

Lecia V. Sequist, MD MPH
[redacted]

AND

Boehringer Ingelheim Pharmaceuticals, Inc
[redacted]

AND

MedWatch 3500A. Please fax to phone number listed on the form.

Please, reference protocol BIBW2992/ IND 110,720 on ALL reports submitted to the FDA and Boehringer Ingelheim Pharmaceuticals.

The Lead Institution will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating all SAEs to all sites conducting the trial.

Participating Institutions must report the AEs to the Protocol Chair and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

6.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The Protocol Chair will review all IND Safety Reports and is ultimately responsible for forwarding the IND Safety Reports to the Participating Institutions. The Participating Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

7.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all Institutions Participating in the DF/HCC Multi-center Protocol.

7.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was *not* prospectively approved by the IRB prior to its initiation or implementation.

7.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations.
The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the Participating Institution's own IRB, per its institutional policy.
A copy of the Participating Institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

8.0 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality control oversight for the DF/HCC Multi-center Protocol.

8.1 Ongoing Monitoring of Protocol Compliance

The DF/HCC Lead Institution will implement monitoring activities from the time before the clinical phase of the protocol begins continuing through to the time of study completion to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution or designee.

The Lead Institution will provide regular and ongoing communication to Participating Institutions about study related information that may include; participation in regular Lead Institution initiated teleconferences, distribution of an ongoing "Newsletter" highlighting overall protocol progress and important announcements, and collecting source documents from Participating Institutions, at specific data points, that support the primary and or secondary endpoints.

Redacted source documents to be sent to the Lead Institution (list does not include baseline source already submitted) for monitoring:

- Day 1 MD/NP/RN notes at start of each new cycle. Documentation of adverse event/grade to be included
- Re-staging exams/reports (cycle 3, 5, 7, etc)
- Upon progression, pathology results from repeat biopsy. Please, refer to page 33, section 7.1.2 and 7.1.3 and Appendix 4 for further details regarding the repeat biopsy.

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution's Coordinators, the Principal Investigators, and the Protocol Chair.

8.2 Evaluation of Participating Institution Performance

8.2.1 Eligibility Checklist:

Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

8.2.2 Accrual of Eligible Participants:

Annual accrual rates for eligible participants enrolled onto therapeutic clinical trials are calculated for each institution. Participating Institutions are expected to maintain the minimum annual average accrual as defined by the protocol grant or contract.

9.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. The main focus in auditing is to measure if the standards and procedures set are being followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and the data were generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the Code of Federal Regulations.

9.1 DF/HCC Sponsored Trials

One audit on-site will be schedule by the QACT assuming at least three subjects have been treated on protocol at the site. Approximately 3-4 subjects would be audited at the site over a 2 day period. If violations which impact subject safety or the integrity of the study are found, more subject records may be audited.

9.3 Participating Institution

It is the Participating Institution's responsibility to notify the DF/HCC Lead Institution of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.4 Coordinating Center (Lead Institution or designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

9.5 Sub-Standard Performance

The Protocol Chair, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.5.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state, federal, and Good Clinical Practice guidelines, will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

Appendix 4

Tissue Sample Shipment Form

DF/HCC Protocol: 10-092

1. Complete the requisition form and include with the sample that is being shipped.

2. Label paraffin block or slides with local surgical specimen number andQACT patient ID (obtained at registration and furnished upon request prior to shipping specimen)

3. Include de-identified pathology report, if available, that is associated with the specimen.

4. E-mail a copy of the Tissue Sample Shipment Form to Beth Kennedy at eakennedy@partners.org. Include the fedex tracking number in the e-mail

5. Ship the slides to: [redacted]

6. Sample Information

   DF/HCC QACT case number: _____

   Surgical Specimen Number w/Local ID: _____

   Date of Collection: _____

   Site of Biopsy: _____

6. Site Contact Information (for questions and specimen return)

   Name/e-mail address: _____

   Site Investigator: _____

   Shipping Address: _____

   _____

Other Medications

If you take any other medications (prescribed or otherwise) please indicate the name of the drug, the dosage taken, and the date taken

Drug	Dose	Date(s) Taken	Reason Taken

If you take a daily medication, please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 1/2/97-2/5/97)

Study Participant Self-Administration Drug Log

Dana-Farber/ Harvard Cancer Care (DF/HCC)

Protocol Number:

Study Participant Name:______________________

Unit Number:__________________
Study ID Number:__________________

Date Dispensed:____________________
Drug A: BIBW 2992

Special Instructions:
We will give you a supply of BIBW 2992 in the form of tablets. You will take your medication (tablets) by mouth, once a day with a glass of water. The study drug should be taken at the same time every morning, one hour before eating breakfast. The pills should not be chewed. You should not skip any doses. On days that you have study visits, you should not take any BIBW 2992 or eat anything prior to your visit. You must bring your supply of BIBW 2992 with you to each study visit. We will ask that you record the time you took your medication on this pill diary
If you miss or vomit a dose, you will not take another dose to replace it. You will take BIBW 2992 every day on a four-week schedule. Each 4 week (28 day) period is called a treatment cycle. There are no breaks from taking BIBW 2992 between cycles. You will continue to take BIBW 2992 until your disease worsens, you experience severe side effects, or you decide to stop study treatment. Please call your study doctor or study nurse if you experience any intolerable side effects. Your dose may need to be stopped for a while and/or reduced.

Study Participant Signature:______________________

Study Drug Log

Please indicate the date, time, drug taken and dosage on the following chart

Drug A: BIBW 2992

Date	Time	Drug A	Dose

Symptoms

Please indicate any symptoms that you may experience during your treatment. Include the date that your particular symptom started and when it ended. Please grade your symptoms according to the following scale:

Grade 1 = Minimal: you are aware of the symptoms, but it did not interfere with normal activities

Grade 2 = Mild: the symptom disrupted normal routine, but required activities were accomplished

Grade 3 = Moderate: the symptom prevented normal activities, but was manageable with prescribed therapies at home

Grade 4 = Severe: the symptom required you to seek further medical intervention

Symptom	Start Date	End Date	Grade

The toxicity grade should reflect the most severe level experienced during the time period