TITLE: Phase I/II study of Dasatinib and Osimertinib in patients with advanced non-small cell lung cancer with EGFR mutations

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Principal Investigator:

Chul Kim, M.D. M.P.H.,

Georgetown Lombardi Comprehensive Cancer Center

3970 Reservoir Road NW Washington DC 20007

Phone: 202-444-1285; E-mail: Chul.Kim@gunet.georgetown.edu

Sub-Investigator(s):

Stephen Liu, M.D., Georgetown Lombardi Comprehensive Cancer Center

Joshua Reuss, MD, Georgetown Lombardi Comprehensive Cancer Center

Jillian Thompson, NP, Georgetown Lombardi Comprehensive Cancer Center

Biostatistician:

Ming T. Tan, Ph.D.

Department of Biostatistics, Bioinformatics, and Biomathematics

Georgetown University, Basic Science 255

Phone: 202-687-0197; E-mail: mtt34@georgetown.edu

Pathologist:

Bhaskar Kallakury, M.D.

Department of Pathology

Georgetown University

Phone: 202) 687-3444; E-mail: KALLAKUB@gunet.georgetown.edu

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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1.0 PRÉCIS

Background

- The treatment of patients with advanced non-small cell lung cancer is unsatisfactory. The median survival is approximately 12 months with standard chemotherapy.
- Epidermal growth factor receptor (EGFR) mutation is one of the most frequent genetic abnormalities observed in non-small cell lung cancer (NSCLC), especially in adenocarcinoma subtype. The most predominant *EGFR* mutations are in-frame deletions in exon-19 and L858R missense mutation, and patients carrying these mutations are mostly sensitive to the EGFR-targeted tyrosine kinase inhibitors (TKIs). However, a significant proportion of patients carrying these sensitizing mutations do not respond well to the first generation EGFR-TKIs (erlotinib and gefitinib), indicating the existence of intrinsic resistance mechanism. Moreover, despite initial response to EGFR-TKIs, acquired resistance is inevitable in all patients.
- Novel treatment strategies need to be developed to overcome resistance to EGFR-TKIs.
- We have recently shown that Cripto-1 overexpression in *EGFR* mutant NSCLC contributes to the intrinsic resistance to EGFR-TKIs through SRC activation. We have also shown that a combination of an EGFR-TKI (both erlotinib and osimertinib) and a Src inhibitor are synergistic in vitro and in vivo in Cripto-1 overexpressing tumors.
- Osimertinib is a third-generation EGFR-TKI, which selectively blocks the activity of *EGFR* mutants but spares that of wild type. The advantage of using osimertinib is that it inhibits not only the mutants of exon-19 deletion and L858R, but also the T790M mutant, which is the most common mechanism of acquired resistance.

- Dasatinib is a potent, orally available ABL1/SRC-TKI, approved for the treatment of chronic myeloid leukemia (CML) in first-line and in patients with imatinib-resistant disease or intolerant, and being actively studied in patients with advanced solid tumors.

Primary objectives

- In the phase I portion of the study, the primary objective will be to determine a safe and tolerable phase II dose of osimertinib and dasatinib in patients with *EGFR* mutant non-small cell lung cancer naïve to EGFR-TKI treatment.
- In the phase II portion of the study, the primary objective will be to determine the rate of non-response to the combination of osimertinib and dasatinib, in patients stratified by Cripto-1 expression in their tumor.

Secondary objectives

- In the phase I portion of the study, the secondary objective will be to describe the pharmacokinetics associated with osimertinib when administered with dasatinib.
- In the phase II portion of the study, the secondary objective will be to determine the median progression free survival (PFS), overall survival (OS), duration of response, and safety and tolerability of this combination regimen.

Eligibility

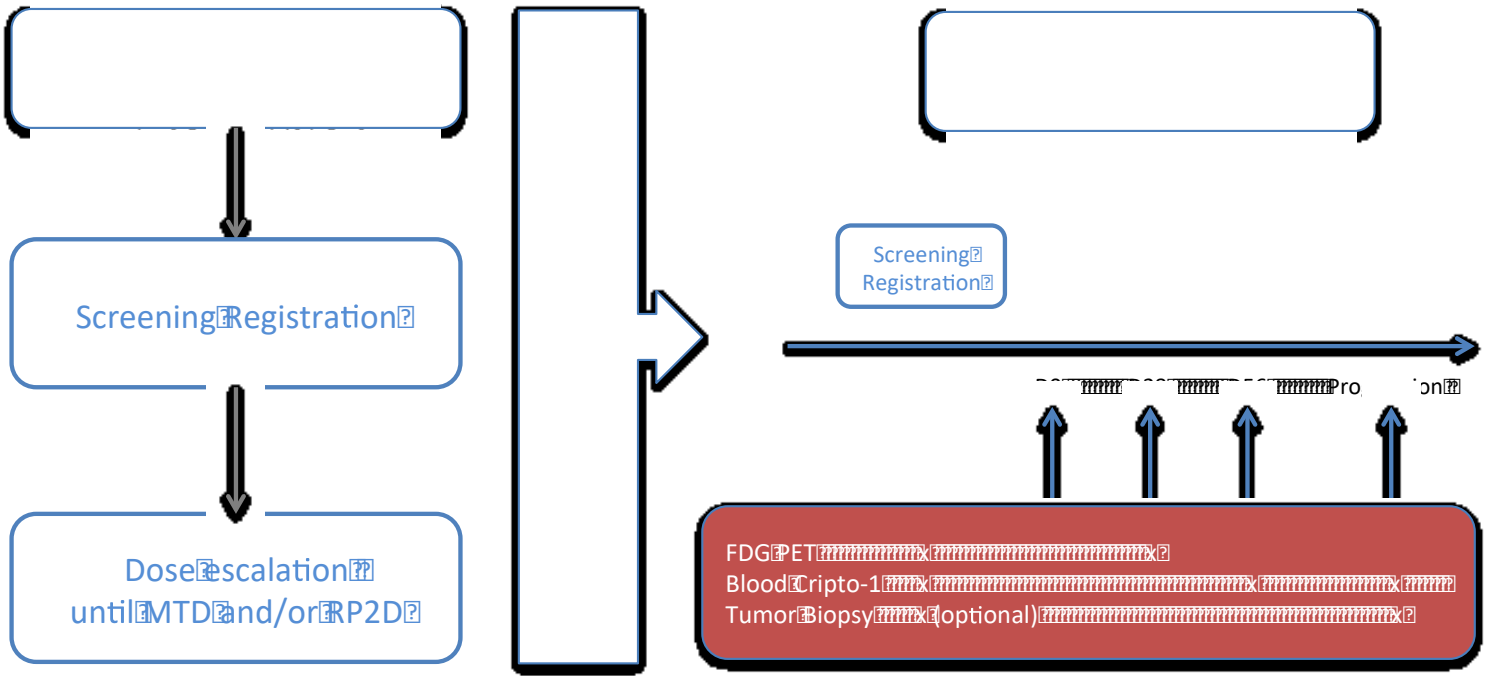
- Patients must have cytologically or histologically confirmed advanced non-small cell carcinoma of the lung.
- Presence of sensitizing *EGFR* mutations (with or without T790M)
- No previous treatment with EGFR-TKIs

- Adequate organ and bone marrow function
- ECOG performance status of 0-2

Design

- Open-label, non-randomized, prospective phase I/II trial
- Following a standard 3+3 design for the phase I portion
- One-sample group sequential multiple testing procedure for the phase II portion

SCHEMA



MTD: Maximum tolerated dose

RP2D: Recommended phase II dose

2.0 BACKGROUND AND RATIONALE

2.1 Non-small cell lung cancer (NSCLC)

2.1.1 Overview of NSCLC

Lung cancer remains the leading cause of cancer deaths among both men and women in the United States. In 2014, 159,260 patients died of lung cancer in the United States, making up 27% of all cancer deaths[1]. The 5-year survival rate for lung cancer (17%) is lower than most of other common solid tumors, such as colon cancer (65%) and breast cancer (89%)[1]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, comprising 86% of all lung cancer cases[2]. Of these patients, more than 55% will present with advanced disease[1], not amenable to curative treatment. Of the remaining 45% that are treated with curative intent, only 20-30% are radically resectable.

Platinum-based doublet chemotherapy regimens are the standard of care for patients with advanced NSCLC and good performance status[3], who do not have targetable driver mutations. The treatment with platinum-based doublet chemotherapy is unsatisfactory, with objective response rates generally in the range of 20-30%[4, 5], and the median survival in the range of approximately 10-12 months[6]. Adding a third chemotherapy drug to the platinum-doublet has not improved overall survival[7]. Non-platinum-based regimens have been evaluated in several trials, but objective response rates were lower compared to platinum-containing regimens[8], and progression-free survival (PFS) was inferior[9].

2.1.2 Targeted therapy for advanced NSCLC

The last decade has seen major advances in the understanding of the genetics and molecular pathogenesis of lung cancer, which led to the advent of targeted therapies. *EGFR* mutation is one of the most frequent genetic abnormalities observed in NSCLC, especially in adenocarcinoma subtype[10]. The most predominant *EGFR* mutations (over 90%) are in-frame deletions in exon 19 and L858R missense mutation[10], and the majority of patients with these mutations have tumors that are sensitive to the EGFR-targeted tyrosine kinase inhibitors. Erlotinib is an orally active reversible epidermal growth factor receptor tyrosine kinase inhibitor, which has demonstrated marked clinical efficacy over standard chemotherapy in *EGFR* mutation-positive advanced NSCLC[11]. Two randomized trials, which compared erlotinib with standard chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive NSCLC, demonstrated objective response rates of 58-83% for erlotinib, and 15-36% for chemotherapy[4, 5]. Median progression-free survival was also significantly longer in erlotinib-treated patients (9.7-13.1 months) than in those treated with chemotherapy (4.6-5.2 months). Erlotinib received approval for the treatment of patients with locally advanced or metastatic NSCLC after failure of one or two chemotherapy regimens by the U.S. Food and Drug Administration (FDA) in 2004[12]. In 2013, the indication for erlotinib was expanded to include first-line treatment of metastatic NSCLC harboring *EGFR* mutations[13]. Erlotinib is well tolerated with most adverse events being grade 1 or 2[14, 15]. The most common side effects of erlotinib are skin rash, diarrhea, and fatigue, which were primarily grade 1 or 2 in severity[4].

2.1.3 Intrinsic and acquired resistance to EGFR-TKIs

Despite remarkable clinical responses to EGFR-TKIs, approximately 10% of patients with *EGFR* mutation-positive NSCLC are refractory to EGFR-TKIs (progression on treatment) [16], and up to 40% of patients harbouring *EGFR* sensitizing mutations do not attain a major response (stable disease of short duration) to the first generation EGFR-TKIs (erlotinib and gefitinib), indicating the existence of intrinsic resistance mechanisms. Furthermore, acquired resistance is inevitable in all patients. Patients develop resistance to EGFR-TKIs in 10-13 months after initiation of EGFR-TKIs[4, 5]. Known acquired mechanisms of resistance to EGFR-TKIs include *EGFR* T790M mutation (50-60%), and much less frequently mutations in *PIK3CA* gene, *MET* gene amplification resulting in ERBB3 signaling, and small cell lung cancer transformation[17-19]. On the contrary, the mechanisms of intrinsic resistance to EGFR-TKIs are relatively unidentified. *KRAS* mutation, *MET* amplification, and high-level hepatocyte growth factor (HGF) expression have been implicated in the molecular pathogenesis of intrinsic resistance to EGFR-TKIs[16, 20].

2.1.4 Role of Cripto-1 in the molecular pathogenesis of resistance to EGFR-TKI

Cripto-1, a member of EGFR-CFC protein family, is also known as teratocarcinoma-derived growth factor-1 (TDGF-1)[21]. Cripto-1 activates phosphatidylinositol 3'-kinase (PI3K)/AKT/glycogen synthase kinase 3β (GSK-3β) and mitogen-activated protein kinase (MAPK) signaling pathways, and functions as a survival factor[22, 23]. High levels of expression of Cripto-1 have been found in a number of human carcinomas

including colorectal, breast, ovarian, and gastric cancers[21]. Overexpression of Cripto-1 was associated with worse prognosis in breast and gastric cancer[24, 25].

We discovered that the expression of Cripto-1 is significantly higher in the *EGFR*-mutated NSCLC tumors from EGFR-TKI-non-responders than in those from responders[26]. We have also demonstrated that Cripto-1 expression contributes to EGFR-TKI (1st generation erlotinib, 2nd generation dacomitinib [26], and 3rd generation osimertinib and CO-1681 inhibitors [unpublished observation]) resistance in lung adenocarcinoma cells *in vitro* (Figure 1A and 1B) and in a mouse xenograft tumor model (Figure 1C) [26]. Both in Cripto-1 transfected lung adenocarcinoma cell lines and primary lung adenocarcinoma cells bearing *EGFR* sensitizing mutations, high Cripto-1 expression correlates with increased levels of SRC phosphorylation (Figure 1B) [26]. Moreover, Cripto-1 was clearly detectable in the medium of Cripto-1 transfected but not mock control lung adenocarcinoma cells (Figure 1D) and the shed Cripto-1 augmented SRC phosphorylation (Figure 1E), suggesting that the shed Cripto-1 may activate SRC signaling. Immunohistochemistry analysis revealed that high Cripto-1 expression correlates with intrinsic erlotinib and gefitinib resistance in *EGFR* mutant lung adenocarcinoma patients (Figure 2A; $p = 0.0001$). High Cripto-1 expression also correlates with worse prognosis in patients with stage I NSCLC (Figure 2B, unpublished observation). The siRNA-mediated depletion of SRC kinase, a downstream effector of Cripto-1, or inhibition with AZD0530, a small molecule Src inhibitor, overcome Cripto-1-induced EGFR-TKI resistance *in vitro* and in xenograft tumors (Figure 2C and 2D) [26]. These findings suggest that 1) Cripto-1 could serve as a surrogate marker to predict EGFR-TKI response and 2) targeting the Cripto-1 pathway may be an effective strategy to combat EGFR-TKI resistance including resistance to the 3rd generation of EGFR

inhibitors (osimertinib and CO-1686) in Cripto-1 positive *EGFR* mutant lung adenocarcinoma. These data suggests that Cripto-1 may be an important contributor to the innate resistance to EGFR-TKIs, and provides a good rationale for targeting both EGFR and Cripto1-SRC pathways to overcome such resistance. Preliminary studies demonstrated an even stronger synergistic antitumor effect when using a third generation EGFR inhibitor (e.g. osimertinib) with a SRC inhibitor. We have generated multiple *EGFR*-mutated NSCLC cell lines stably expressing Cripto1, along with their mock controls. Using these model systems, we have acquired data showing that osimertinib (from a commercial source) can synergize with dasatinib, a SRC inhibitor, to inhibit *in vitro* tumor cell proliferation (Figure 3).

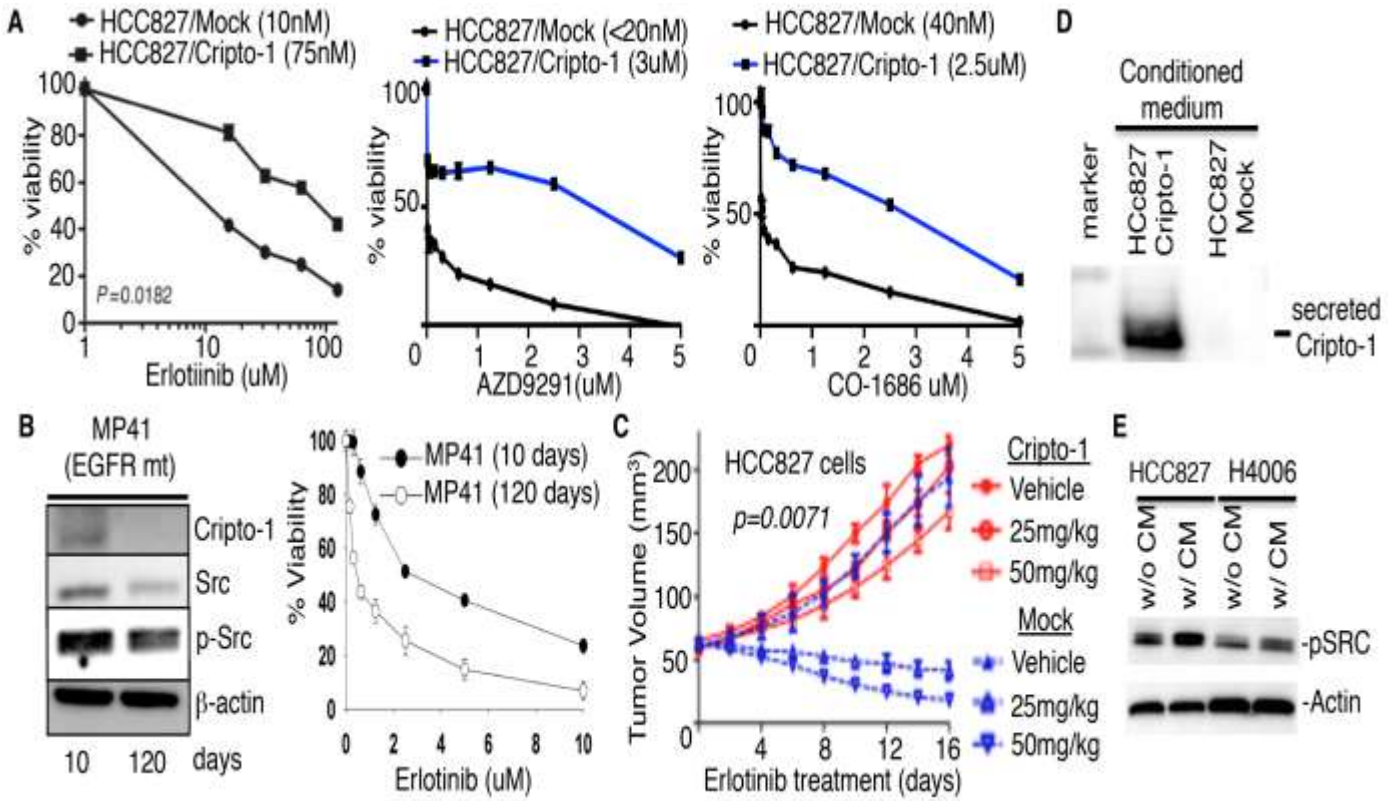


Fig 1. A. Exogenous expression of Cripto-1 renders *EGFR* mutant HCC827 lung adenocarcinoma cells resistant to erlotinib, Osimertinib and CO-1686 *in vitro*. CellTiter Glo assays were performed 72 hours

after erlotinib treatment. Data represent the mean ± SD of triplicate measurements relative to untreated cells. P value was calculated using paired 2-tailed t test. IC_{50}s are shown in parentheses. **B.** Progressive loss of Cripto-1 expression in primary cells (MP41), derived from an intrinsic erlotinib resistant lung adenocarcinoma patient carrying *EGFR* L858R mutation, correlates with increasing sensitivity to erlotinib. Note that the progressive loss of Cripto-1 expression is accompanied by concomitant reduction of total SRC and phospho-SRC. **C.** Cripto-1 renders *EGFR* mutant lung adenocarcinoma HCC827 xenografts resistant to erlotinib in immunocompromised mice. **D.** Shedding of Cripto-1. Cripto-1 western blot of concentrated cell culture media of Cripto-1- and mock-transfected HCC827 lung adenocarcinoma cells. **E.** Conditioned medium of Cripto-1-transfected HCC827 cells induced SRC phosphorylation of Cripto-1 negative HCC827 and H4006 cells. w/ CM or w/o CM, with or without conditioned medium treatment.

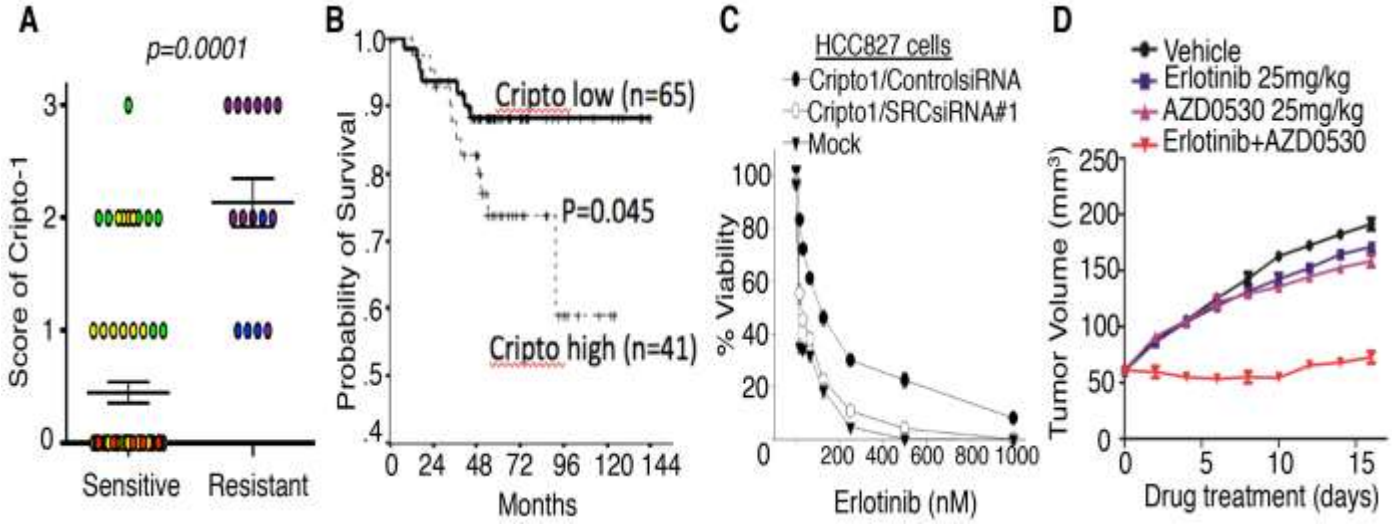


Fig 2. A. High Cripto-1 expression (determined by immunohistochemistry) correlates with intrinsic erlotinib and gefitinib resistance in *EGFR* mutant NSCLC patients (n=85; p=0.0001). **B.** Cripto-1 expression correlates with worse prognosis in stage I NSCLC. Recurrence–free survival was analyzed in 106 radically resected stage I NSCLC patients according to levels of Cripto-1 expression by immunohistochemistry. **C.** Inhibition of SRC by siRNA-mediated knockdown reinstates erlotinib

sensitivity of Cripto-1-transfected *EGFR* mutant HCC827 cells. **D.** AZD0530 sensitizes *EGFR* mutant HCC827Cripto-1 xenografts to erlotinib in immunocompromised mice.

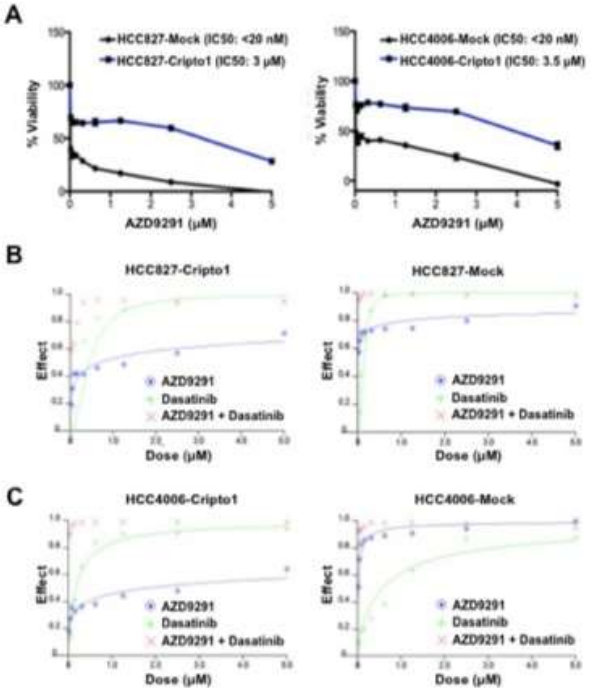


Fig 3. The effect of osimertinib on the Cripto-1 expressing/*EGFR*-mutated NSCLC cells with/without Dasatinib combination. A) Ectopic Cripto-1 expression drastically desensitizes *EGFR*-mutated NSCLC tumor cells to osimertinib treatment, as determined by the CellTiter-Glo Luminescent Cell Viability Assay. IC50 for each cell line is shown in the parenthesis. B) Dasatinib resensitizes Cripto-1 expressing cells (HCC827-Cripto1 and HCC4006-Cripto1) to osimertinib, and the combination results in a synergistic inhibitory effect *in vitro*.

2.2 Osimertinib

2.2.1 Non-clinical studies of osimertinib

Osimertinib is a potent, selective, orally active, irreversible inhibitor that targets both sensitizing and T790M *EGFR* mutations[27]. In EGFR recombinant enzyme assays

(Millipore), osimertinib had approximately 200 times greater potency against L858R/T790M than wild-type EGFR, suggesting its wide selectivity margin. Compared to both first (erlotinib and gefitinib) and second generation (afatinib and dacomitinib) EGFR-TKIs, osimertinib demonstrated comparable potency in inhibiting EGFR phosphorylation in EGFR cell lines harboring activating *EGFR* mutations (PC-9, H3255, H1650). Importantly, osimertinib was much more potent in inhibiting EGFR phosphorylation in EGFR cell lines (H1975, PC-9VanR) carrying T790M mutation with mean IC_{50} less than 15 nmol/L.

Osimertinib showed dose-dependent tumor regression in both PC-9 (ex19del) and H1975 (L858R/T790M) tumor xenograft models[27]. In both models, tumor shrinkage was observed at doses as low as 2.5 mg/kg/day after 14-day treatment. The response to osimertinib was shown to be durable in tumor xenograft models. In PC-9 xenografts, there was a complete response following 40 daily doses of 5 mg/kg/day osimertinib, which lasted more than 200 days. By comparison, gefitinib at 6.25 mg/kg/day resulted in less tumor regression, and tumors began to regrow after nearly 90 days in the same xenograft model. The activity of osimertinib was further examined in *in vivo* transgenic mouse models. Tumors harboring $EGFR^{L858R}$ were sensitive to afatinib and osimertinib, but tumors carrying $EGFR^{L858R+T790M}$ were only sensitive to osimertinib.

Osimertinib is metabolized into at least two metabolite species, AZD5104 and AZ7550[27]. Biochemical assays showed that AZD7550 had a similar potency and selectivity profile to osimertinib, whereas AZD5104 exhibited significantly greater potency than osimertinib across mutant and wild-type EGFR assays, and thus displayed a smaller margin of selectivity against wild-type EGFR compared to EGFRm/T790M and EGFRm in vitro. Osimertinib has good bioavailability, and wide tissue distribution.

When tumor tissues from H1975 xenografts were harvested 1, 6, 16, 24, and 30 hours after a single dose of osimertinib (5mg/kg), both phospho-EGFR and downstream signaling pathway were inhibited after 6 hours. Although osimertinib had a half-life of approximately 3 hours after oral dosing in the mouse model, phospho-EGFR staining remained reduced even after the 30-hour time point, which was consistent with the fact that osimertinib is an irreversible inhibitor of EGFR. Osimertinib was well tolerated in the animals. There was minimal weight loss, which was defined as less than 5% loss of baseline body weight, even after administration for 200 days.

2.2.2 Clinical studies of osimertinib

The mesylate salt of osimertinib has been evaluated in a phase I dose-escalation clinical trial in patients with advanced *EFGR*-mutant NSCLC who progressed after treatment with EGFR-TKIs[28]. The study included dose-escalation and dose expansion cohorts. Patients in the dose-escalation cohort received a single oral dose of osimertinib, which was followed by a period of pharmacokinetic evaluation. After 7 days, the patients received the same dose of osimertinib in an oral form for the remainder of the study. Additional pharmacokinetic assessment was performed while patients were receiving daily continuous dosing. The first dose level was 20 mg daily. If there was evidence of clinical activity in a dose-escalation group, a dose-expansion cohort could be opened. In the dose-escalation cohorts, daily dosing of osimertinib was initiated immediately.

A total of 253 patients from 33 sites were enrolled in the study[28]. 31 patients were treated in dose-escalation cohorts, and 222 patients were enrolled to dose-expansion cohorts. The dose range of osimertinib used in the dose-escalation cohorts was from 20 mg to 240 mg. The first dose level of 20 mg was selected based on the preclinical data.

The most common side effects included diarrhea, rash, nausea, and anorexia. Most of the adverse effects were grade 1 or 2. There was an increased incidence of adverse effects, most notably at the 160 mg and 240 mg dose levels. There were 6 cases of potential pneumonitis-like events. All 6 patients discontinued osimertinib at the time of the event, and received steroid treatment with subsequent resolution or improvement of symptoms. There were 6 patients who developed hyperglycemia, and 11 patients who had prolongation of QTc (corrected QT) interval; none of these events led to discontinuation or reduction of osimertinib. Fatal adverse events were observed in 7 patients, and it was reported that one case (pneumonia) was possibly drug-related. Pharmacokinetic analyses showed that osimertinib had a median time to reach the maximum observed concentration (Cmax) of 6 hours, and a mean half-life of 55 hours. Based on this information, it was estimated that steady-state concentrations would be reached within 22 days of daily dosing.

Among 239 evaluable patients, 123 (51%) had a confirmed complete response (1 patient) or partial response (122 patients)[28]. 78 (33%) had stable disease, 34 (14%) had progressive disease, and 4 (2%) were unevaluable for response. The response rate was comparable at each dose level. *EGFR* T790M was detected in tumors from 138 of the 222 patients (62%). Of the 138 patients, 127 patients were evaluable for response. The objective response rate was seen in 78 of the 127 patients (61%) in patients with *EGFR* T790M. The objective response rate in patients without *EGFR* T790M was 21% (13 of the 61 patients). Of the 105 patients in the dose-expansion cohorts who had a confirmed response, 85% had responses lasting equal to or longer than 6 months, and the median progression free survival was 8.2 months. Based on the safety and efficacy data from the

phase I study, the recommended first dose level of osimertinib for phase II and III studies (NCT02094261, NCT02296125) was 80 mg daily.

The preliminary data of osimertinib as first-line therapy for patients with advanced NSCLC with *EGFR* mutations who were naïve to EGFR-TKI treatment were presented at the 51th annual meeting of the American Society of Clinical Oncology (ASCO)[29]. In this trial, a total of 60 patients were treated with osimertinib at doses of 80 mg daily (n=30) and 160 mg daily (n=30). At the time of data analysis, the median duration of follow-up was 9.6 months. osimertinib was well tolerated with most adverse events being grade 1 or 2. Most common adverse events were rash, diarrhea, dry skin, stomatitis, paronychia, decreased appetite, and fatigue. The incidences of hyperglycemia, QT prolongation, and interstitial lung disease (ILD)-like events were 5%, 7%, and 5%, respectively. Dose reduction due to adverse events occurred in 10% of patients treated with 80 mg daily and 43% of those treated with 160 mg daily. 3 (10%) patients treated with 80 mg daily and 1 (3%) patient treated with 160 mg daily discontinued osimertinib due to adverse events. The objective response rate in patients treated with 80 mg daily was 63% with all responses being partial response. In the group receiving 160 mg daily, 83% had objective responses with 1 (3%) complete response and 24 (80%) partial responses. The percentages of patients remaining progression-free at 9 months were 83% in patients receiving 80 mg daily and 78% in those receiving 160 mg daily.

In 2015, osimertinib was approved by the FDA for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR-TKI therapy.

2.3 Dasatinib

2.3.1 Non-clinical studies of dasatinib (from the Dasatinib Investigator's Brochure, Version 15, June 2015)

Detailed information on all nonclinical studies performed to date can be found in the Investigator's Brochure (IB). A brief summary of preclinical studies is as follows. Dasatinib is an orally bioavailable synthetic small molecule inhibitor of the SRC-family protein-tyrosine kinases, and it also inhibits c-KIT and PDGFR-ß. Dasatinib binds to and inhibits the growth-promoting activities of these kinases. Apparently because of its less stringent binding affinity for the BCR-ABL kinase, dasatinib has been shown to overcome the resistance to imatinib of CML cells harboring BCR-ABL kinase domain point mutations, although not the T315I gatekeeper mutation [30]. Dasatinib induces apoptosis in lung cancer cells which are dependent on the *EGFR* mutation status: *EGFR* mutant cells are much more sensitive to dasatinib (IC_{50} of 100 to 250 nmol/L) than the wild type EGFR cells (IC_{50} >10μmol/L)[31]. Apoptosis induced by dasatinib was associated with down-regulation of Akt and STAT3[31]. Preclinical pharmacokinetics of dasatinib have been examined in mice, rats, dogs, and monkeys. Dasatinib underwent metabolism via various mechanisms including hydroxylation, N-oxidation, N-dealkylation, glucuronidation and sulfation. No unique metabolites were found in humans. Dasatinib was mainly excreted in feces with a small portion found in urine. With respect to toxicology, there were no toxicities that would hinder the administration of dasatinib to humans.

2.3.2 Clinical studies of dasatinib (from the Dasatinib Investigator's Brochure, Version 15, June 2015)

Dasatinib is a second-generation BCR-ABL1 inhibitor, approved for the treatment of patients with newly diagnosed CML or intolerant, and in imatinib-resistant disease. The absorption of dasatinib is rapid. The median time to reach Cmax is 0.45 to 3.2 hours. Dasatinib has wide distribution to the extravascular space and is metabolized by cytochrome P450 3A4 in humans. The mean half-life of dasatinib ranges from 3 to 5 hours, and is not affected by dose administration interval. Adverse effects described in patients treated with dasatinib include myelosuppression, fluid retention, pleural effusion, gastrointestinal disorders, fatigue, headache, musculoskeletal disorders, rash, infection and less frequently pulmonary hypertension[30].

The efficacy of single-agent dasatinib has been studied in several phase II trials in patients with advanced NSCLC. In a phase II study of patients with unselected advanced NSCLC, a total of 34 patients received dasatinib as first-line treatment[32]. The first 22 patients were treated with 100 mg twice a day. Due to pleural effusion and fatigue, the remainder of the patients received 100 mg in the morning and 50 mg in the evening. Out of 34 patients treated, there was only one responder and that was wild-type EGFR. This patient obtained a complete metabolic response by FDG-PET (2-deoxy-2-(^{18}F)fluoro-D-glucose positron emission tomography) scanning, despite treatment being stopped after only 12 weeks due to malaise. Response continued without treatment for over 28 months. The incidence of grade 2-3 pleural effusion and fatigue was 44% and 27%, respectively. Another phase II study gave dasatinib at 70 mg twice a day in patients with *EGFR* mutant adenocarcinoma who progressed on an EGFR-TKI (acquired resistance). After a protocol amendment, patients were kept on the EGFR-TKI to which dasatinib

was added at 100 mg once daily. There were no responses out of a total of 21 patients treated (9 under the original design and 12 after amendment)[33]. Pleural effusions were a significant side effect with four patients requiring chest tube placement. A phase II study by Brunner et al. in patients with squamous cell carcinoma of the lung was halted after 5 patients were enrolled due to excessive toxicity[34].

These data indicate that dasatinib has substantial toxicity in NSCLC patients at high doses and that in unselected patients activity as a single agent is modest.

2.4 Rationale for the combination of EGFR-TKI and SRC inhibitor

SRC is the prototypic member of a family of proto-oncogenic tyrosine kinases collectively known as SFKs (Src Family of Kinases), which includes Fyn, Yes, Fgr, Hck, Lck and Lyn[35]. SRC has multiple regulatory functions and has been implicated in pathways regulating bone metabolism, proliferation, angiogenesis, invasion and metastasis[36]. SRC is involved in signaling from many receptor tyrosine kinases, including EGFR, PDGFR, HGFR and others. High expression and activity of SRC has been correlated with advanced malignancy and poor prognosis in a variety of human cancers[37]. Expression of SRC in lung cancer has been found to be high in over 50% of lung cancers of different histologies[38].

Several SRC inhibitors have been developed for the treatment of cancer, but activity has been modest so far. Saracatinib (AZD0530), a potent oral inhibitor of the SRC family at nanomolar concentrations, has been tested in a phase II study in patients with advanced NSCLC who had progressed after one line of chemotherapy with or without an EGFR inhibitor [39]. Of the 37 patients who were included, 2 patients experienced a partial response, one had a tumor with an *EGFR* exon 19del mutation and the other was

wild type for EGFR and K-Ras. The development of Saracatinib (a relatively selective SRC inhibitor) in cancer has however been halted by AstraZeneca.

The concept of combining TKIs against EGFR and SRC has recently been tested in advanced NSCLC, with the combination of erlotinib and dasatinib. In a phase I/II study in advanced pretreated NSCLC patients, erlotinib was given alone for a week, followed by co-administration of dasatinib[40]. The dose-escalation cohorts consisted of cohort 1 (dasatinib 50 mg twice daily and erlotinib 100 mg once daily), cohort 2 (dasatinib 50 mg twice daily and erlotinib 150mg once daily), cohort 3, dasatinib 70mg twice daily and erlotinib 150 mg once daily), and cohort 4 (dasatinib 140 mg once daily and erlotinib 150 mg once daily). Erlotinib at a dose of 150 mg daily and dasatinib at 70 mg twice daily were the maximum tolerated dose (MTD) and recommended doses for phase II testing. The most common side effects were GI toxicities such as diarrhea (88%), anorexia (71%), and nausea (79%). Only two patients had grade 3 diarrhea. Acneiform rash was a frequent adverse effect, but only two events were grade 3. Regarding hematologic toxicity, 53% had anemia (two events of grade 3), 29% had thrombocytopenia (one event of grade 3), and 65% had lymphopenia (6 events of grade 3). 35% of patients had pleural effusions, but all were grade 2 or less and no patient required thoracentesis or pleurodesis to treat drug-related effusions. Lastly, 74% had fatigue, but there were no grade 3 episodes. The steady-state pharmacokinetics of erlotinib were not affected by dasatinib. Of 34 patients included in the study, 2 experienced a partial response, one short lasting in a patient with an *EGFR* mutation and another response of over a 14-month duration in a patient with wild-type EGFR squamous cell carcinoma. This tumor was later found to bear a DDR2 kinase domain mutation. Dasatinib is known to be able to inhibit DDR2 to some extent[41]. Interestingly, a phase I/II study of the same

combination in untreated patients with advanced solid tumors (phase I) and advanced NSCLC (phase II) demonstrated 5 partial responses out of 35 patients (14%), all of whom had advanced NSCLC with activating *EGFR* mutations[42]. In this study, the MTD was erlotinib 150 mg daily and dasatinib 70 mg daily based on the phase I proportion of the study.

These clinical studies indicate that SRC inhibitors have a low level of activity as single agents in unselected NSCLC patients and the combination of a SRC inhibitor and an EGFR inhibitor might be potentially of interest, but the selection of patients is important. The clinical experience with the combination of erlotinib and dasatinib suggests that *EGFR* mutant lung cancer is where the activity is most expected. Together, preclinical data[31], the clinical experience with the combination of erlotinib and dasatinib[40], and our finding of important synergy between the SRC inhibitor dasatinib and osimertinib in reverting intrinsic EGFR resistance due to Cripto-1 overexpression in *EGFR* mutant adenocarcinoma[26], leads us to hypothesize that selecting patients with *EGFR* mutant adenocarcinoma of the lung will be crucial in order to have activity of this combination. This study proposes to explore the feasibility and benefit of combining osimertinib with a SRC inhibitor (dasatinib) for treating Cripto-1-positive *EGFR*-mutated NSCLC patients. The advantage of using osimertinib is that it not only inhibits the exon 19 deletion and L858R mutants, but also the T790M mutant. In addition, osimertinib appears overall to be better tolerated than erlotinib.

3.0 STUDY HYPOTHESIS AND OBJECTIVES

3.1 Hypothesis

The combination of osimertinib with dasatinib is feasible and will decrease the rate of non-response in *EGFR*-mutant NSCLC patients who have not received an EGFR-TKI before. In particular, and more precisely, the combination of osimertinib and dasatinib will reduce the proportion of patients who progress or have stable disease lasting 4 months or less (intrinsic resistance). Secondary endpoints will be time to progression, overall survival, and tolerability of the combination.

3.2 Primary Objectives

3.2.1 The primary objective of the phase I portion is to determine the maximum tolerated dose and recommended phase II doses of osimertinib when given in combination with dasatinib in patients with advanced NSCLC with *EGFR* mutations.

3.2.2 The primary objective of the phase II portion is to determine the rate of non-response (progressive disease or stable disease lasting 4 months or less) to the combination of osimertinib and dasatinib in patients with *EGFR* mutations (including T790M), who have not received an EGFR-TKI before, stratified by Cripto-1 expression in their tumor.

3.3 Secondary Objectives

3.3.1 To characterize the safety profile for the combination of osimertinib and dasatinib

3.3.2 To describe the pharmacokinetics associated with osimertinib when administered with dasatinib.

3.3.3 To determine progression-free survival, overall survival, and duration of response after treatment with the combination of osimertinib and dasatinib.

3.4 Exploratory Objectives and Correlative Studies

Because the data of the correlation of Cripto-1 expression with intrinsic resistance to EGFR-TKI are retrospective[26], a prospective study will be needed to confirm these findings. Ideally, only patients with high Cripto-1 expression in their tumors would be the subject of this study. This, however, would require a validated and Clinical Laboratory Improvement Amendments (CLIA)-certified test to be able to prospectively allocate patients to treatment. We will therefore treat all patients with the combination of osimertinib and dasatinib, and then stratify patients based on Cripto-1 expression assessed post-treatment. Because the overall response rate and non-responder rate to osimertinib is similar to erlotinib, and all patients treated with single agent osimertinib are expected to develop resistance, a combination approach to all patients with *EGFR* mutations is reasonable. We will also evaluate the relationship between Cripto-1 levels and patients' response to drug treatment.

Cripto-1 expression will be assessed in all patients on tumor samples, obtained before treatment with osimertinib and dasatinib, using an immunohistochemistry method that has been developed in our previous study[26]. Based on our own research[26] and prior studies[43], Cripto-1 expression is expected to be present in the majority of samples, but high expression (score 2-3) will be present in less than 50% of the positive cases[26]. We will correlate the Cripto-1 expression in the baseline sample with response to treatment.

In addition, whenever feasible, fresh tumor biopsies will be obtained before starting treatment and at progression. These biopsies will be analyzed for Cripto-1 expression by RT-PCR and/or immunohistochemistry as described in our recent publication[26], before treatment and at progression. Briefly, quantitative RT-PCR will be performed using Cripto-1 primers described in our previous studies[26], the specificity of which has already been and will be revalidated in Cripto-1-positive/Cripto-3-negative (H727) and Cripto-3 positive/Cripto-1 negative cells as described in our previous study[26]. If sufficient biopsy material is available, we will determine the phosphorylation status of SRC by western blot using the anti-phospho-SRC Tyr416 (Cell Signaling) antibody described in our paper[26], in parallel with Cripto-1 expression study.

In collaboration with Dr. David S. Salomon at the National Cancer Institute (NCI) in Bethesda, Maryland, levels of plasma Cripto-1 will be assessed using a validated ELISA with a rabbit monoclonal antibody against the NH2-terminus of human Cripto-1 that can measure as little as 1 ng of Cripto-1 in plasma and serum and that can detect both free Cripto-1 or Cripto-1 bound to known protein partners such as GRP78, Alk4 or Nodal. The Cripto-1 ELISA assay is specific for Cripto-1 and is linear from 1 ng to 100 ng of Cripto-1. ELISA assays will be performed on plasma or serum samples from patients before treatment, after 8 weeks and at the time of progression. The shed Cripto-1 levels in blood of patients will not be a direct evidence of inhibition of the intrinsic EGFR resistance, because the study will use a combination of EGFR and SRC-TKIs, but it will potentially be a valuable marker of efficacy and a way to monitor treatment effect.

In addition, we will investigate whether the PK of osimertinib is influenced by dasatinib. Finally, we will assess whether FDG-PET performed at day 28 will predict responses to osimertinib and dasatinib, compared to baseline FDG-PET.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Patients must have cytologically or histologically confirmed advanced NSCLC. Patients with mixed histology containing a small cell lung cancer component are not eligible.

4.1.2 Patients must have adequate archival material from a previous biopsy to determine *EGFR* mutation status and Cripto-1 expression, or undergo a biopsy of fresh tissue of the primary cancer or a metastatic site in order to make these determinations, if archival material is not available.

4.1.3 Presence of sensitizing *EGFR* mutations (deletion in exon 19, L858R in exon 21, G719X, and L861Q). Patients with the T790M mutation will also be eligible.

4.1.4 No prior treatment with an EGFR TKI for the advanced NSCLC.

4.1.5 ECOG performance status of 0-2.

4.1.6 Patients must have measurable disease by RECIST criteria, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan. See Section 7.1.2 for the evaluation of measurable disease.

4.1.7 Prior systemic treatment is allowed, but toxicities of prior therapy must be resolved to grade 1 or less as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.1.8 Adequate organ and bone marrow function (hemoglobin $\geq$ 9 g/dL; absolute neutrophil count $\geq$ 1.5 x 10^9/L; platelet counts $\geq$ 100 x 10^9/L; serum bilirubin $\leq$ 2 x ULN; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 2.5 x ULN or $\leq$ 5 x ULN if liver metastases; calculated creatinine clearance $\geq$ 50 mL/min or normal creatinine (as defined as serum creatinine not exceeding the upper normal limit as defined by the performing laboratory)).

4.1.9 No uncontrolled arrhythmia; no myocardial infarction in the last 6 months.

4.1.10 Life expectancy of at least 12 weeks.

4.1.11 Age > 18 years.

4.1.12 Ability to understand and willingness to sign a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Patients who have had immunotherapy or chemotherapy during the previous 4 weeks (6 weeks for nitrosoureas or mitomycin) before treatment, or those who have ongoing toxic manifestations of previous treatments, with the exception of alopecia, of grade higher than 1. Patients who have had whole brain radiation therapy (WBRT) during the previous 2 weeks before treatment (no washout period is required for patients who have received stereotactic body radiation therapy).

4.2.2 Major thoracic or abdominal surgery from which the patient has not sufficiently recovered yet.

4.2.3 Untreated and uncontrolled second tumor in the past 2 years.

4.2.4 Logistical or psychological hindrance to participation in clinical research.

4.2.5 Patients with untreated symptomatic brain metastases may be eligible if symptoms do not require urgent surgery or radiation, and no steroids are necessary.

4.2.6 Patients with evidence of interstitial lung disease (bilateral, diffuse, parenchymal lung disease).

4.2.7 Pleural or pericardial effusions of any grade at study entry. Subjects previously diagnosed with pleural/pericardial effusion of any grade resolved at the time of study entry are allowed.

4.2.8 Ability to become pregnant (or already pregnant or lactating). Women and men who want to participate have to agree to use two highly effective forms of contraceptive prior to study entry, for the duration of study participation, and for 30 days following completion of therapy, to be eligible. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

4.2.9 At high medical risk because of non-malignant systemic disease including uncontrolled infection.

4.2.10 Known to be serologically positive for hepatitis B, hepatitis C or HIV.

4.2.11 Uncontrolled or significant cardiovascular disease, including any of the following:

- QTc interval > 480 msec (mean value and manually verified) at 3 or more time points within a 24 hour period if necessary.
- Diagnosed or expected congenital long QT syndrome.
- Concurrent congestive heart failure, prior history of class III/IV cardiac disease (New York Heart Association).
- Left ventricular ejection fraction < 50%
- Prior history of cardiac ischemia or cardiac arrhythmia within the last 6 months. Coronary angioplasty or stenting in the previous 12 months.
- Any history of second or third degree heart block (may be eligible if the subject currently has a pacemaker).
- Uncontrolled hypertension defined as inability to maintain blood pressure below the limit of 140/90 mmHg.
- Known pulmonary hypertension.

4.2.12 History of significant bleeding disorder unrelated to CML, including:

- Diagnosed congenital bleeding disorders (e.g. von Willebrand's disease)
- Diagnosed acquired bleeding disorder within one year (e.g. acquired anti-factor VII antibodies)

4.2.13 Any other medical condition that in the Investigator's opinion would not make the patient a good candidate for the study.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

5.1.1 Phase I

5.1.1.1 Dose Limiting Toxicity (DLT)

The dose limiting toxicity (DLT) period consists of one cycle, 28 days. Dose-limiting toxicity is defined as adverse events occurring during the first cycle of therapy and related to the study drugs (attributions: possible, probable, and definite) while fulfilling one of the following criteria as per CTCAE version 4.03:

- Any grade 3 or 4 toxicity except for grade 3 diarrhea, nausea, or vomiting if it can be controlled with supportive therapy
- Persistent (>21 days) non-hematologic grade 2 adverse events despite optimal medical management and treatment delay > 21 days

5.1.1.2 Dose Escalation and Treatment Duration

Treatment will be administered on an outpatient basis. A standard dose-escalation phase I design will be used. Selection of the starting dose of osimertinib in combination with dasatinib is based on the results from previous clinical studies. Since osimertinib is the known active drug for *EGFR*-mutant NSCLC, the dose of osimertinib will be the recommended phase II dose of 80 mg/day. Dose escalation will only include 2 dose levels; in addition there will be 2 dose levels below the starting dose level if dose

reductions are necessary. A typical targeted DLT level is 30%, thus we will utilize the classical 3+3 design. So three subjects will be enrolled at each dose level in the absence of DLT. If 0 of 3 have DLT at DL2 (see Table 1), a total of 6 patients will be enrolled at DL2. If 1 of 3 patients experiences a DLT at a given dose level, that dose level will be expanded to a maximum of 6 patients. If 2 patients in a dose level of 3 or 6 patients experiences DLT, then the MTD will have been exceeded and the next lower dose level will be expanded to 6 patients, if needed. MTD will be the highest dose at which 0-1 of 6 patients experience a DLT. If a patient does not complete cycle 1 for any reason other than DLT, the patient will not be evaluable for DLT and will be replaced at that dose level. Patients who develop a DLT will be de-escalated by one dose level (DL). There is no limit to the number of cycles a patient can receive.

Table 1. Dose-escalation schedule

Dose-Escalation Schedule		
Dose Level (DL)	**Osimertinib dose (Oral)**	**Dasatinib (Oral)**
Level -2	80 mg	50 mg once daily
Level -1	80 mg	70 mg once daily
Level 1 (starting doses)	80 mg	50 mg twice daily
Level 2	80 mg	70 mg twice daily

5.1.1.3 Patient Replacement

Three patients within a dose level must be observed for one cycle (28 days) before accrual to the next higher dose level may begin. If a patient is withdrawn from the study prior to completing 28 days of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level.

5.1.2 Phase II

Determination of the recommended phase II dose will be based on the MTD, tolerability, and toxicities beyond cycle 1. Courses are defined as 28 days of dosing. There is no limit to the number of cycles a patient can receive.

5.2 General Management of Toxicities

Any patient who receives treatment on this protocol will be evaluable for toxicity. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Once a patient has a dose reduction due to toxicity, the dose will not be re-escalated. General guidelines for the management of toxicities are described in Table 2 and Table 3. In the case of toxicity, supportive treatment should be used (e.g. anti-emetics, anti-diarrheals).

5.2.1 Hematologic Toxicities

Since osimertinib is associated with hematologic toxicity to a lesser extent than dasatinib and it is the known active drug for *EGFR*-mutant NSCLC, dasatinib will be dose modified first as described in Table 2. Osimertinib will be dose reduced as per Table 4 if hematologic toxicity is refractory to discontinuation of dasatinib, meaning that the hematologic toxicity recurs or persists even after discontinuation of dasatinib.

Table 2. General Recommendations for Dose Modification and Management of Hematological Toxicities

Adverse Event or Observation	Dose Modification at a given dose level
ANC* $\geq 750/mm^3$ AND	Maintain dose

Platelets ≥ 75,000/mm^3 AND Hemoglobin ≥ 8 g/dL	
ANC 500-750/mm^3 OR Platelets 50,000-75,000/mm^3 OR Hemoglobin 6-8 g/dL	1. Hold dasatinib until ANC ≥ 750/mm^3, platelets ≥ 75,000/mm^3, and hemoglobin ≥ 8 mg/dL. Initiate appropriate medical therapy**. 2. Resume treatment at the original starting dose. 3. On second occurrence, repeat step 1. 4. On third occurrence, reduce one dose level and resume treatment.
ANC < 500/mm^3 OR Platelets <50,000/mm^3 OR Hemoglobin < 6 g/dL OR Anemia with life-threatening consequences***	1. Hold dasatinib until ANC ≥ 750/mm^3, platelets ≥ 75,000/mm^3, and hemoglobin ≥ 8 mg/dL. Initiate appropriate medical therapy. 2. Study drug(s) may be restarted at one DL lower. 3. On second occurrence, discontinue dasatinib.

*ANC: Absolute neutrophil count

** Growth factors to prevent neutropenia will not be administered prophylactically, but can be used during a drug hold to assist the recovery. Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤ 10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3. Red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL or the patient is symptomatic.

*** Rare reports of aplastic anaemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anemia including but not limited to

persistent fever, bruising, bleeding, and/or pallor. If signs and symptoms suggestive of aplastic anemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anemia.

5.2.2 Non-hematologic Toxicities

For non-hematologic toxicities, dose reductions will be allowed, with the aim of maintaining a full dose of osimertinib and reducing primarily dasatinib unless the toxicity is clearly associated with osimertinib (see Table 3). If dose reduction of osimertinib is indicated, osimertinib will be dose reduced as per Table 4.

Table 3. General Recommendations for Dose Modification and Management of Non-Hematological Toxicities

Event	AE Grade or Observation	Dose Modification
Dermatology/Skin	Grade 1 or 2	Maintain dose.
	Grade 3 or 4 OR Intolerable Grade 2	1. Hold the drug(s) causing the toxicity until ≤ tolerable grade 2. 2. Study drug(s) may be restarted at one DL lower. 3. On second occurrence, repeat step 1.
	Recurrent Grade 3 after 2 dose reductions	Discontinue the drug(s) causing the toxicity.
	Grade 4	Discontinue the drug(s) causing the toxicity.
Diarrhea	Grade 1 or 2	Maintain dose. Supportive treatment with anti-diarrheal treatment (e.g. Loperamide 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free for 12 hours).
	Grade 3 or 4	Hold the drug(s) causing the toxicity until ≤

		tolerable grade 2. Reduce one dose level and resume treatment.
	Recurrent Grade 3 or 4	Hold the drug(s) causing the toxicity until ≤ tolerable grade 2. Reduce one additional dose level and resume treatment.
	Recurrent Grade 3 or 4 after 2 dose reductions	Discontinue the drug(s) causing the toxicity.
Liver Function (serum bilirubin, AST/ALT)	Grade 1 or 2	Maintain dose.
	Grade 3 or 4	Hold the drug(s) causing the toxicity until grade 2, then reduce one dose level and resume treatment.
	Recurrent Grade 3 or 4	Hold the drug(s) causing the toxicity until ≤ grade 2. Reduce one additional dose level and resume treatment.
	Recurrent Grade 3 or 4 after 2 dose reductions	Discontinue the drug(s) causing the toxicity.
Pulmonary Toxicities*	ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac**	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec[a] within 3 weeks of withholding osimertinib, then restart at a reduced dose (40 mg) or at 80 mg (at the discretion of the investigator).
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
Other non-hematologic toxicity*** (Please see the footnotes for further guidance on keratitis, and	Grade 1 or 2	Maintain dose.
	Any grade 2 of concern	Hold the drug(s) causing the toxicity until grade 1, then reduce one dose level and resume treatment.
	Grade 3 or 4	Hold the drug(s) causing the toxicity until grade 2, then reduce one dose level and resume treatment.
	Recurrent Grade 3 or 4	Hold the drug(s) causing the toxicity until grade 2. Reduce one additional dose level and resume

erythema multiforme/Stevens-Johnson syndrome)		treatment.
	Recurrent Grade 3 or 4 after 2 dose reductions	Discontinue the drug(s) causing the toxicity.

* Pleural effusion: Dasatinib is associated with fluid retention including pleural effusion. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest imaging. Grade 3 or 4 pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events are typically managed by supportive care measures that include diuretics and short courses of steroids.

*ILD/Pneumonitis-like toxicity: If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease/pneumonitis is observed, an interruption in study treatment dosing is recommended, and the Sponsor study team should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic oedema or pulmonary hemorrhage. The results of full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters) will be captured by eCRF. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of interstitial lung disease should be considered and study treatment permanently discontinued.

**Cardiac toxicity

- Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and osimertinib has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during

treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

- Osimertinib will be withheld if ejection fraction decreases by 10% from pretreatment values and is less than 50%. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, osimertinib will be permanently discontinued.
- In light of the potential for QT changes associated with osimertinib, electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) must be correct to be within normal ranges prior to first dose and electrolyte levels monitored during study treatment. Patients with QTcF prolongation to >500 msec should have study treatment interrupted and regular ECGs performed until resolution to <481 msec or recovery to baseline if baseline QTcF is >481 msec and then restarted at a reduced dose of 40 mg, or 80mg at the discretion of the investigator. If the toxicity does not resolve to ≤ grade 1 within 21 days of withholding osimertinib the patient will be permanently withdrawn from study treatment. If QTc interval prolongation with signs/symptoms of serious arrhythmia occurs, osimertinib will be permanently discontinued.

***Keratitis: Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

***Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS): Case reports of Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been

uncommonly and rarely reported, respectively, in association with osimertinib treatment. Before initiating treatment, patients should be advised of signs and symptoms of EM and SJS. If signs and symptoms suggestive of EM develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. If signs and symptoms suggestive of SJS appear, osimertinib should be interrupted or discontinued immediately.

Table 4. Osimertinib Dose Level Reductions

Dose Level (DL)	**Osimertinib dose (Oral)**
Starting Dose	80 mg once daily
First dose reduction	40 mg daily

5.3 Concomitant Medications/Treatments

Treatment with other anticancer therapy or any other investigational agent is prohibited from 30 days prior to the first dose of Osimertinib and dasatinib, and throughout the study.

5.4 Off-treatment criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression*
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Any severe (grade 3 or 4) toxicity that has not resolved to NCI/CTEP grade 1 toxicity by three weeks or by medical judgment of the PI or one of the associate investigators discontinuation is considered to be in the best interest for the patient.
- For osimertinib, interstitial lung disease/pneumonitis and QTc elevation with signs or symptoms of serious arrhythmia are unacceptable adverse events.

- Patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the patient unfit for further treatment in the judgment of the investigator.
- Patient is non-compliant with the protocol guidelines

* Patients are allowed to stay on treatment beyond progression if the investigator thinks that the patient is still benefiting from the treatment.

5.5 Off-study criteria

- Death
- Patient refuses follow-up or decides to withdraw consent from the study

5.6 Duration of Follow-Up

Patients will remain on the study and be followed for adverse events after removal from treatment for minimum of 4 weeks after the final dose of osimertinib and/or dasatinib. Patients who were removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed for progression of the disease and survival.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Subjects who meet all eligibility criteria will be enrolled in the study. Assessments performed exclusively to determine eligibility for this study will be done after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. All screening procedures must be performed within 4 weeks prior to starting study drugs unless otherwise stated. The screening procedures include:

- Complete history and physical examination including vital signs, height, weight and ECOG performance score (see appendix A).
- Baseline imaging studies: Patients should have a baseline radiographical evaluation with whole-body FDG-PET scan and contrast-enhanced computed tomography (CT) scan of the chest/abdomen/pelvis. Baseline brain imaging will also be obtained via either MRI or CT of the brain with contrast. Outside imaging studies will be accepted at the discretion of the PI.
- A baseline chest x-ray (optional if chest CT is performed)
- Electrocardiogram (EKG)
- Echocardiogram or multigated acquisition (MUGA) scan to assess left ventricular ejection fraction
- Laboratory evaluation (baseline tests to be obtained within one week prior to starting treatment unless otherwise noted)

- Hematological Profile: Complete blood count (CBC) with differential and platelet count, prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT).
- Biochemical Profile: Sodium, potassium, calcium, phosphorous, magnesium, blood urea nitrogen (BUN), creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactic acid dehydrogenase (LDH), bilirubin, albumin.
- Baseline glomerular filtration rate (GFR) calculation.
- Serum or urine beta-hCG for female patients of childbearing age within 24 hours prior to the start of study drug.
- Plasma or serum Cripto-1

6.2 Procedures During Treatment

Patients will be followed every two weeks for the first 4 weeks and the following will be done.

Prior to Each Treatment Cycle:

- History and physical exam
- Laboratory evaluation: Hematologic and biochemical profile
- EKG

Once treatment tolerance has been established, patients will be seen every 4 weeks, or more frequently if medically indicated.

- Tumor imaging will be performed every 2 cycles (within a week of starting the next cycle). Scans may be extended to every 3 cycles at the discretion of the investigator, if the subject has remained stable on treatment.
- Echocardiogram or multigated acquisition (MUGA) scan will be performed as clinically indicated.
- FDG-PET will be repeated 4 weeks (cycle 1 day 28 ± 2 days) after initiation of study drugs in order to assess the metabolic response.
- Plasma or serum for detection of shed Cripto-1 will be obtained at 8 weeks and at tumor progression.
- In consenting patients, a fresh tumor biopsy will be obtained at disease progression to assess Cripto-1 expression by RT-PCR and/or immunohistochemistry.

After 30 days from treatment termination, the following will be obtained:

- History and physical exam
- Laboratory evaluation: Hematologic and biochemical profile
- EKG

7.0 Measurement of Effect

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

[44]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST version 1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with osimertinib and dasatinib.

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

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

7.1.2 Disease Parameters

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

Note: Tumor lesions that are located in a previously irradiated area might or might not be considered measurable at the discretion of the PI.

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

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

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

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

Conventional CT and MRI: CT and MRI - CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. For this study helical Multidetector CT will be performed with cuts of 5 mm in slice thickness for chest, abdomen and pelvis lesions and 2-3 mm thickness for head and neck lesions.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up may be a sign of progressive disease. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease (PD). If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site. If so, the date of PD will be the date of the initial abnormal FDG-PET scan. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A positive FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of target lesions, taking as reference the baseline sum diameters. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if

that is the smallest on study). The appearance of one or more new lesions is also considered progression).

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.

7.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

7.1.4.3 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 patient's best

response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 3. Evaluation of patients with measureable disease

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

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

Note:
Patients 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 patients with non-measureable disease

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR

Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

7.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

7.1.7 Overall Survival

Overall survival is defined as the duration of time from start of treatment to death from any cause.

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

AEs should be reported up to 30 days following the last dose of study drug. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention

- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

8.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. The term 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious Adverse Events

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor*, it results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization, excluding hospitalizations done to facilitate research studies or for non-medical reasons (to facilitate completion of protocol-directed requirements, i.e. biopsy, imaging, desensitization for platinum)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Potential drug induced liver injury (DILI)**
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is a serious adverse event.
- Adverse Events (AEs) for new malignant tumors (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study) reported during a study should generally be assessed as Serious AEs.

If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history, and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy

*Dr. Chul Kim is the sponsor of this trial.

**Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.1.5 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

Attribution categories are 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.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- The adverse event resolves or the symptoms or signs that constitute the adverse

event return to baseline;

- Any abnormal laboratory values have returned to baseline;
- There is a satisfactory explanation other than the study drug for the changes observed; or
- Death.

8.3 Reporting Requirements for Adverse Events

8.3.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug. The Sponsor-Investigator can be contacted at Chul Kim, MD, E-mail: Chul.Kim@gunet.georgetown.edu, phone: 202-444-2223 with CC to LCCC-Multicenter-IITs@georgetown.edu.
- The institutional officials must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR). UPRs are defined as any problem or event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.
- The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.3.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.4 Reporting of Serious Adverse Events (SAEs) to Astra Zeneca (AZ)

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

* Investigative site must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

* ***Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox*** ***AEMailboxClinicalTrialTCS@astrazeneca.com*** ***(email is preferred method)***

or

* ***Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-888-984-7229***

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator

is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution*. All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

8.5 Reporting of Serious Adverse Events (SAEs) to Bristol-Myers Squibb (BMS)

8.5.1 Serious Adverse Event Collection and Reporting

See Appendix B for mandatory adverse event reporting information. All serious adverse events must be reported to BMS Worldwide Safety.

8.5.2 Special Warnings and Precautions for Use

8.5.2.1 Reproductive status

- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
- Women must not be breastfeeding.

- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug, plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion.
- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion.
- Azoospermic males and WOCBP, who are not heterosexually active, are exempt from contraceptive requirements. However, WOCBP must still under pregnancy testing as described in this section.
- Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective contraception. Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly.
- At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below.

8.5.2.2 Highly effective methods of contraception

- Male condoms with spermicide

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner (previous language flexible as appropriate per Directive as based on current knowledge of effects of study drug(s) on hormone exposures and as agreed upon by MST Lead and Medical Monitor in consultation with the compound Lead Clinical Pharmacologist.). Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard
- Vasectomy
- Complete Abstinence*

Note: *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

8.5.2.3 Less effective methods of contraception

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide

- Progestin only pills by WOCBP subject or male subject's WOCBP partner (inclusion flexible as appropriate per Directive as based on current knowledge of effects of study drug (s) on hormone exposures and as agreed upon by MST Lead and Medical Monitor in consultation with the compound Lead Clinical Pharmacologist)
- Female Condom (A male and female condom must not be used together)

8.5.2.4 Prohibited and/or Restricted Treatments

Medications associated with QT interval prolongation that are prohibited on this study include:

- Quinidine, procainamide, disopyramide
- Amiodarone, sotalol, ibutilide, dofetilide
- Erythromycins, clarithromycin
- Chlorpromazine, haloperidol, mesoridazine, thiordazine, pimozide
- Cispride, bepridil, droperidol, methadone, arsenic, chlorquine, domperidone, halofantrine, levomethadyl, penamidine, sparfloxacin, lidoflazine.

8.5.2.5 Other Restrictions and Precautions

- Caution should be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants. Antiplatelet agents or anticoagulants should be avoided in the setting of Grade 3 or 4 thrombocytopenia.
- Ideally, subjects should not be taking other medications known to prolong the QT interval. However, should the investigator believe that therapy with a

potentially QT prolonging medication is vital to an individual subject's care, then additional ECG(s) should be done at the investigator's discretion to ensure the subject's safety.

- Dasatinib is a substrate and an inhibitor of cytochrome P450 (CYP) 3A4. Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving dasatinib.
- Additionally, strong to moderate CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may significantly increase concentrations of dasatinib and should be used with caution when administered concurrently with dasatinib.
- Strong to moderate CYP3A4 inducers (e.g. rifampicin) may decrease the concentration of dasatinib and should be used with caution when administered concurrently with dasatinib.

9.0 DRUG INFORMATION

9.1 Osimertinib

- Classification and Mode of action: Osimertinib is a third-generation, selective, irreversible inhibitor that targets both sensitizing and *EGFR* T790M mutations.
- Storage: The product should be stored in the pack provided and used

according to the instructions on the label.

- Protocol dose: Whole tablets should be administered and swallowed whole with a glass of water during the morning at the same time each day. The dose for this study starts 80 mg orally once daily.
- Route of administration for this study: oral
- Incompatibilities: Not applicable
- Availability: Provided by sponsor
- Side effects:
    - Based on the phase I study by Janne et al., most of the adverse effects were grade 1 or 2[28]. The incidences of grade 3-5 diarrhea, rash, nausea, and anorexia were 2%, 1%, 1%, and 2%, respectively. There were 6 cases of potential pneumonitis-like events. There were 6 patients who developed hyperglycemia, and 11 patients who had prolongation of QTc (corrected QT) interval; none of these events led to discontinuation or reduction of osimertinib.
    - Please refer to the IB for further details about the side effect profile of osimertinib.

9.1.1 Drug accountability

The investigator, or a responsible party designated by the investigator, must maintain careful record of the inventory and disposition of all agents received from AstraZeneca. A member of the research team will be documenting pill counts at each visit and patients will be required to bring their bottles to every visit and return any unused pills when they go off-study. Patients going off-study must return unused pills to the research team.

9.2 Dasatinib

- Other names for the drug(s): SPRYCEL®, BMS-354825
- Classification and mode of action: a potent, broad-spectrum adenosine triphosphate (ATP) competitive inhibitor of multiple critical oncogenic tyrosine kinases and kinase families, including BCR-ABL, SRC, c-KIT, platelet-derived growth factor (PDGF) receptor, and ephrin receptor kinases
- Storage and stability:
    - SPRYCEL (20, 50, 80, 100, and 140 mg) or dasatinib film-coated tablets (5, 20, and 50 mg) should be stored at 15° to 25°C (59° to 77°F).
    - Dasatinib for oral suspension may be stored at 15° to 30°C (59° to 86°F).
- Protocol dose: Whole tablets should be administered and swallowed whole with a glass of water during the morning and evening at the same time each day. The dose for this study starts 50 mg orally twice daily, with the potential for higher doses with higher dose levels or lower dose levels.
- Route of administration for this study: Per oral
- Incompatibilities: Not applicable
- Availability: Provided by sponsor
- Side effects: Refer to the agent's package insert for a comprehensive list of adverse events.
    - In a phase II study of dasatinib in patients with advanced NSCLC[32], the most common grade 3 toxicity was dyspnea (44%) caused by underlying disease, chronic obstructive pulmonary disease, and/or

pleural effusion. The incidences of grade 2 and 3 pleural effusion were 26% and 18%, respectively. Grade 2 nausea occurred in 6% of the patients. There was no grade 3 nausea. 6% of the patients developed grade 2 or 3 rash. Lymphopenia was the most common hematologic adverse effect (grade 2 in 15% of the patients, grade 3 in 3% of the patients). 6% of the patients had grade 2 or 3 anemia. There was no thrombocytopenia or neutropenia. Significant laboratory abnormalities were infrequent. The most common non-hematologic adverse effect was elevated AST/ALT (grade 2 in 6% of the patients).

PRODUCT INFORMATION TABLE

Product Description

Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty)/Label Type**	**Appearance**	**Storage Conditions (per label)**
Dasatinib	20mg, 50mg	Various packaging configurations Open label	Not applicable	White to off-white, biconvex, film-coated tablets	Refer to label on container or package insert/summary of product characteristics

9.2.1 Drug accountability

The investigator, or a responsible party designated by the investigator, must maintain careful record of the inventory and disposition of all agents received from Bristol-Myers

Squibb. A member of the research team will be documenting pill counts at each visit and patients will be required to bring their bottles to every visit and return any unused pills when they go off-study. Patients going off-study must return unused pills to the research team.

9.3 Unused Study Drug and Destruction

A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request. Unused study drug not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

10.0 CORRELATIVES/SPECIAL STUDIES

10.1 Pharmacokinetics

During the phase I portion of the study, pharmacokinetics for osimertinib will be assessed.

10.1.1 Timeline

Blood samples will be collected at the following times.

- Baseline Pre-dose Day 1
- Post-dose Day 1: 2 hours; Post-dose Day 1: 4 hours Post-dose Day 1: 6 hours
- Pre-dose Day 1, Cycle 2; Post-dose Day 1, Cycle 2: 4 hours
- Pre-dose Day 1, cycle 3, and then every cycle pre-dose

10.1.2 Procedure

- Samples will be analyzed using an ultra high-performance liquid chromatography (HPLC), validated for processing human samples.
- The samples are to be drawn, **immediately** placed on wet ice, refrigerated, and serum and plasma will be separated, aliquoted and stored at -20 C until shipment.
- The sample label should contain the following information: Cycle number, Day number, time after dosing, and exact draw date and time.
- Blood samples (7ml green top [heparin] tube) for osimertinib measurement by HPLC will be drawn according to the above timeline. [Osimertinib will be assessed by Covance Laboratories. Details for shipment will be provided as part of a Laboratory Manual.]
- Blood samples (7ml green top [heparin] tube) for dasatinib measurement by HPLC will be drawn according to the above timeline.

10.2 Pathology Correlative Studies

Acknowledging the difficulties in obtaining fresh tumor samples in NSCLC due to the location of tumors being mostly within the thorax, utilization of existing tumor biopsy samples (mainly from the initial diagnosis, and/or surgery) will be allowed. If the patient's tumor tissue is unavailable, then the patient will be evaluated for repeat biopsy prior to enrollment in the study. If the patient refuses or the patient's tumor is located in a position that places the patient at increased risk, then the patient may not be eligible for the study.

10.2.1 Timing*

Tumor biopsies will be performed at the following times.

- Prior to treatment on C1D1
    - Mandatory if there is no archival material that can be used to determine *EGFR* mutation status and Cripto-1 expression in order to be eligible for the study
    - When archival tumor material is available, a fresh tumor biopsy is optional.
- Optional – at the time of progression

*Biopsies may be not performed on the specific dates and times due to the following reasons, including but not limited to, delayed recovery of hematologic toxicities, delayed clinic schedule, or national holidays.

10.2.2 Tissue sampling and Handling

A block of archival tumor material will be requested from each patient. If no archival material is available, fresh material will be obtained. A resection sample or blocks of tissue from the original resection are requested. Where a block cannot be released by the governing pathology department, 5 x 6µm re-cuts on charged slides will be requested. Samples from participating institutions will be shipped as described below.

- Archival material will be sent from outside institution to the Georgetown University Medical Center via FedEx at room temperature. Testing will be performed at:

    Bhaskar Kallarury, M.D.

    Department of Pathology

Lombardi Comprehensive Cancer Center

Georgetown University

3970 Reservoir Road NW Washington DC 20007

- If a fresh tumor biopsy is obtained, the biopsy samples are to be immediately embedded, frozen, and stored in Dr. Giaccone's lab at -80°C on site.

  Giuseppe Giaccone, M.D., Ph.D.

  Department of Oncology

  Lombardi Comprehensive Cancer Center

  Georgetown University

  3970 Reservoir Road NW Washington DC 20007

- Each patient sample set will be assigned a unique patient identifier. The protocol scientific investigator(s) handling the samples will be blinded as to the patient identification, patient data and outcome.

10.2.3 Studies

- Cripto-1 expression on tumor samples obtained before treated with Osimertinib and dasatinib using an immunohistochemistry method that has been developed[26].
  - The formalin-fixed, paraffin-embedded (FFPE) tumor specimen will first be H&E-stained and evaluated by a pathologist to ensure the tumor content. FFPE slides will undergo antigen retrieval (Dako Target Retrieval Solution) followed by staining with human rabbit anti-Cripto-1 antibody

(Rockland) at 1:2500 dilution. Samples will be scored by a pathologist according to overall intensity of the staining using a 0-3 scoring system.

- Whenever feasible, fresh tumor biopsies will be obtained before starting treatment and at progression. These biopsies will be analyzed for Cripto-1 expression by RT-PCR and/or immunohistochemistry. Quantitative RT-PCR will be performed using Cripto-1 primers as described in our previous study[26].
- If sufficient biopsy material is available, we will determine the phosphorylation status of SRC by western blot using the anti-phospho-SRC Tyr416 (Cell Signaling) antibody as previously described[26], in parallel with Cripto-1 expression study.
- EGFR mutational analysis will be performed on pretreatment tumor samples at Dr. Giaccone's lab.

10.3 Serum Correlative Studies

10.3.1 Timing

Subjects consented to participate will provide blood samples at the following time points.

- Baseline Pre-dose Day 1
- Pre-dose Day 1, Cycle 3
- At the time of disease progression

10.3.2 Tissue sampling and Handling

Each patient sample set will be assigned a unique patient identifier. Blood samples needed for the measurement of plasma Cripto-1 levels will be sent to Dr. Giuseppe Giaccone's lab. Details on shipment will be provided in a Laboratory Manual.

10.3.3 Studies

- Levels of plasma Cripto-1 will also be assessed using a validated ELISA with a rabbit monoclonal antibody against the NH2-terminus of human Cripto-1

10.4 FDG-PET

In order to assess whether FDG-PET performed at day 28, compared to baseline FDG-PET, will predict responses to osimertinib and dasatinib, two FDG-PET scans will be obtained.

10.4.1 Timing

- Baseline FDG-PET scan to be obtained within 14 days prior to starting treatment
- Cycle 1 Day 28 (±2 days)

10.5 Specimen Banking

Patient samples collected for this study will be retained in the Dr. Giaccone's lab. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Dr. G. Giaccone will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Georgetown University Medical Center. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This study is a dual-agent open-label phase I/II study of dasatinib and osimertinib. The phase I portion will follow a standard dose-escalation phase I design as described in section 5.1.1.2. The primary endpoint of the phase I part is to determine a safe and tolerable phase II dose of osimertinib and dasatinib based upon DLTs. Once the MTD/RP2D is determined, the study will accrue patients for the phase II portion. The endpoint of the phase II part is the reduction of the proportion of patients who progress or have stable disease lasting 4 months or less (intrinsic resistance).

11.2 Sample Size and Accrual

The null hypothesis that the proportion of patients who progress or have stable disease lasting 4 months or less is at least 30% will be tested against a one-sided alternative. The null hypothesis is based on the fact that 37% of treatment-naïve patients treated with osimertinib at a dose level of 80 mg once daily had either stable disease or progressive disease as their best response. We would like to reject the null hypothesis with 85% power at a significance level of 5% when the true proportion of patients who progress or have stable disease ≤ 4 month is 10%. A two-stage (group sequential) design with a total of 28 patients will be used. This flexible multistage design (developed by the study

statistician and his colleagues), has operating properties similar to that of the Simon's two-stage designs but offers flexibility in monitoring and interim analysis should the planned schedule be varied[45]. It allows an early assessment of statistical evidence for both efficacy and futility, and provides a discordance probability that an early trend could be reversed should the trial continue to enroll all 28 patients. At the first stage, 14 patients will be entered. If 4 or less patients progress or have stable disease for ≤ 4 months, then an additional 14 patients will be enrolled in the second stage; If 5 or more of the 14 patients in the first stage progress or have stable disease for ≤ 4 months, we will conclude that the therapy is not sufficiently active in this patient population. The protocol will be amended to reflect this conclusion. If no one among the first 14 patients progress or have stable disease for ≤ 4 months, we conclude there is already adequate statistical evidence that the therapy is active in this patient population and continue to enroll additional 14 patients to allow to be treated with this promising regimen. The chance for a reversal of the conclusion either for efficacy or for futility based on this decision rule is less than 2% (the discordance probability). At the completion of the second stage, if 4 or less among the 28 patients progress or have stable disease for ≤ 4 months, we conclude that the therapy is active in this patient population, and otherwise it is not.

Progression-free survival (PFS) is another very important endpoint in this study. Since there are relatively few successful Phase III trials in the disease studied here, we are only interested in detecting a large PFS time difference between the proposed treatment and historical control in this single arm early stage trial so as to increase the chance for Phase III success. The median PFS time is about 10 months based on current historical control data, and we are interested in an improvement of 10 months in median

PFS time to merit a treatment improvement that is considered promising. With 28 patients determined from the primary outcome, we will have 83% power at a significance level of 0.05 to detect an improvement of 10 months in median PFS time from historical control. This power calculation was based on uniform accrual over time in 18 months, 12 months follow up, no loss to follow-up and exponentially distributed progression times.

It is expected that at least 10% of the newly diagnosed patients with advanced NSCLC will potentially be eligible for this study. At Georgetown, approximately 150-200 new lung cancer cases are seen each year. The addition of Hackensack and the Military Hospital should allow to be accruing at a rate of 2-3 patients a month. This will allow accrual of 28 patients in approximately 18 months.

11.3 Data Analyses Plans

The proportion of patients who progress or have stable disease lasting 4 months or less will be estimated as a binomial proportion with 95% exact confidence interval. The progression-free and overall survival functions will be estimated and plotted by the Kaplan–Meier method. In addition, the median progression-free and overall survival times will be reported along with the 95% confidence intervals. We will compare the levels of Cripto-1 shed into the blood stream of the patients enrolled in the phase I/II study of the combination of osimertinib and dasatinib, with an external cohort of patients treated with erlotinib alone by the nonparametric Wilcoxon rank-sum test. Comparisons of baseline plasma Cripto-1 levels and levels during treatment will be made using the Wilcoxon signed-rank test. Cripto-1 expression levels in plasma and tumor will be compared, and the relationship between Cripto-1 expression in plasmas/tumors and patients' response to drug treatment will be determined with the Pearson's correlation

coefficient and logistic regression, respectively. These tests will allow assessing whether changes in Cripto-1 in the blood might be a good surrogate for resistance to EGFR inhibition. The populations for analysis will include a safety population and a Pharmacokinetic population.

- Safety population: All subjects who receive at least 1 dose of study medication. Only subjects with clear documentation that no study medication was received may be excluded from analysis. This population will be used for all summaries of safety data (AEs, concomitant medications, laboratory data).
- Pharmacokinetic population: All subjects who have a PK profile.

All statistical tests will be two-sided, and considered statistically significant when the p-value is less than 0.05. All statistical analyses will be performed using SAS (Version 9.4; SAS Institute, Cary, NC).

12.0 STUDY MANAGEMENT

12.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form.

Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

12.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Research office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

12.3 Registration Procedures

All patients must be registered with the Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Study Coordinator at each site. All patients must be registered with the Georgetown CMO (Clinical Research Management Office) before enrollment to study. Prior to registration, eligibility criteria must be confirmed by the Georgetown Multi-Site Study Coordinator. To register a patient, the following documents should be completed by the research nurse or data manager and faxed or emailed to the Coordinating center:

Attn: Hilary Allen, fax 202-6872399, E-mail HKA10@georgetown.edu

1) Subject Registration Form ? Eligibility Checklist
2) All source documents for inclusion/exclusion criteria

12.4 Data Management and Monitoring/Auditing

The Principle Investigator and the Co-Investigators will review the data including weekly safety monitoring. The investigators shall meet on a weekly basis to review toxicities and follow up on results of patients enrolled on the study.

Progress on the trial and the toxicities experienced will be reviewed by a Data and Safety Monitoring Board (DSMB) of three clinicians who are not investigators on the study. The DSMB will review toxicity data on a monthly basis and will communicate any concerns about the trial to the DSMC Chair who will then schedule a meeting with the investigator to discuss the concerns and develop an action plan to address them The monthly reports which are reviewed and signed off on by the DSMB will be forwarded to the Data and Safety Monitoring Committee (DSMC). The DSMC will meet quarterly to

review the progress and toxicity of the study. Results of the DSMC meetings will be forwarded to the IRB.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to close the study to further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons, or that a study be closed early due to slow accrual, the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC, then the Lombardi Cancer Center Director must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the Lombardi Cancer Center Director will be responsible for reaching a mutually acceptable decision about the study.

Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision.

12.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

12.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

12.5.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

12.5.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected

- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

12.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an

amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site

personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix A. ECOG Performance Status Score

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

Appendix B. Mandatory Adverse Event Reporting Information for Dasatinib

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse

Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

- Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

For studies conducted under an Investigator IND in the US include the following:

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH

5600 Fishers Lane

Rockville, MD 20852-9787

Fax: 1-800-FDA-0178 (1-800-332-0178)

http://www.accessdata.fda.gov/scripts/medwatch/

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

A **nonserious adverse event** is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days

following the last dose of study treatment. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such. The following laboratory abnormalities should be documented and reported appropriately:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g. dose tapering if necessary for subject safety). The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in

accordance with SAE reporting procedures. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]. Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Appendix C. Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the electronic case report form (eCRF).

1. Drugs Inducing CYP3A4 Metabolism That AstraZeneca Strongly Recommend Are Not Combined With Osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes. A drug-drug interaction study of osimertinib evaluated in patients showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any patient receiving osimertinib.

Drugs Inducing CYP3A4

Contraindicated drugs	Withdrawal period prior to osimertinib start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

2. Medicines Whose Exposures May be Affected by Osimertinib That AstraZeneca Considers May be Allowed With Caution

Osimertinib may increase the concentration of sensitive BCRP and Pgp substrates (concentration of the sensitive BCRP substrate, rosuvastatin and sensitive Pgp substrate, fexofenadine, are increased).

Exposure, Pharmacological Action and Toxicity May be Increased by Osimertinib

Warning of possible interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with osimertinib.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	
Dabigatran	
Aliskiren	
Digoxin	

3. Drugs That May Prolong QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics website: https://www.crediblemeds.org/. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP).

During screening the drugs that patients are currently receiving (prescription and non-prescription) should be checked against the ArizonaCert website. In addition, drugs intended for use following study treatment initiation should be checked against the website.

3.1 Drugs with a known risk of Torsades de Pointes

Drugs in this category are known to prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended

3.1.1 Before commencing study treatment

Drugs in the category of known risk of TdP must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 3.

3.1.2 During study treatment

It is recommended that drugs in the category of known risk of TdP are not co-administered with study treatment (osimertinib) and for a period of two weeks after

discontinuing study treatment, however if it is considered essential for patient management to co-administer these drugs with study treatment (osimertinib) close monitoring of ECGs and electrolytes is recommended.

The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the CredibleMeds® website (https://www.crediblemeds.org/) to provide the most up to date information.

Table 3 Drugs with a known risk of TdP[a]

Drug name	Withdrawal period prior to study treatment start
Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide[b], Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

a. This list should be checked against the full and most current list presented in the CredibleMeds® website (https://www.crediblemeds.org/).

b. Estimated value as pharmacokinetics of arsenic trioxide has not been studied.

Other TdP risk Categories

Patients receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for patient management and the patient has been stable on therapy. Close monitoring of ECGs and electrolytes is recommended.

Patients with **congenital long QT syndrome (CLQTS) are excluded** from this study.

Guidance regardless of TdP risk category

Following study treatment initiation if it is considered essential for patient management to give drugs known to prolong QTc interval, **regardless of TdP risk category**, close monitoring of ECGs and electrolytes is recommended.