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Title: A Pilot Study of Local Ablative Therapy for Treatment of Oligoprogressive, EGFR-Mutated, Non-Small Cell Lung Cancer (NSCLC) After Treatment with Osimertinib (AZD9291, Tagrisso)

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Commercial Agent

Drug Name:	**Osimertinib (AZD9291, Tagrisso)**
IND Number:	Not Applicable - IND Exempt
Manufacturer:	AstraZeneca

PRÉCIS

Background:

- EGFR tyrosine kinase inhibitors (TKI) have significantly improved the response rate (RR) and survival in patients with tumors harboring EGFR-sensitizing mutations.
- An invariable consequence of treatment with EGFR-TKIs is the development of acquired resistance. The most common mechanism of resistance observed in approximately 50% of all cases is the emergence of a secondary mutation (T790M) in exon 20.
- Osimertinib is a third-generation EGFR-TKI designed to target the T790M mutation, which has shown impressive responses in both first- and second-line settings.
- Despite these developments, it is almost certain that selection pressure will lead to the emergence of newer clones that are resistant to treatment with osimertinib. In fact, a newly identified EGFR mutation (C797S) that results in acquired resistance to osimertinib has been reported recently.
- The use of local ablative therapies for patients who develop limited metastatic disease (oligoprogressive disease) on EGFR-TKI therapy is promising.
- We hypothesize that following local ablative therapy to treat oligoprogressive disease after emergence of resistance to AZD9291, osimertinib can be resumed safely and re-initiation of osimertinib results in additional progression-free survival benefits.

Objectives:

- Determine the safety, tolerability, and efficacy (as assessed by PFS) of re-initiation of osimertinib following local ablative therapy (LAT) for patients with oligoprogressive disease after treatment with osimertinib
- Assess mechanisms of acquired resistance to osimertinib

Eligibility:

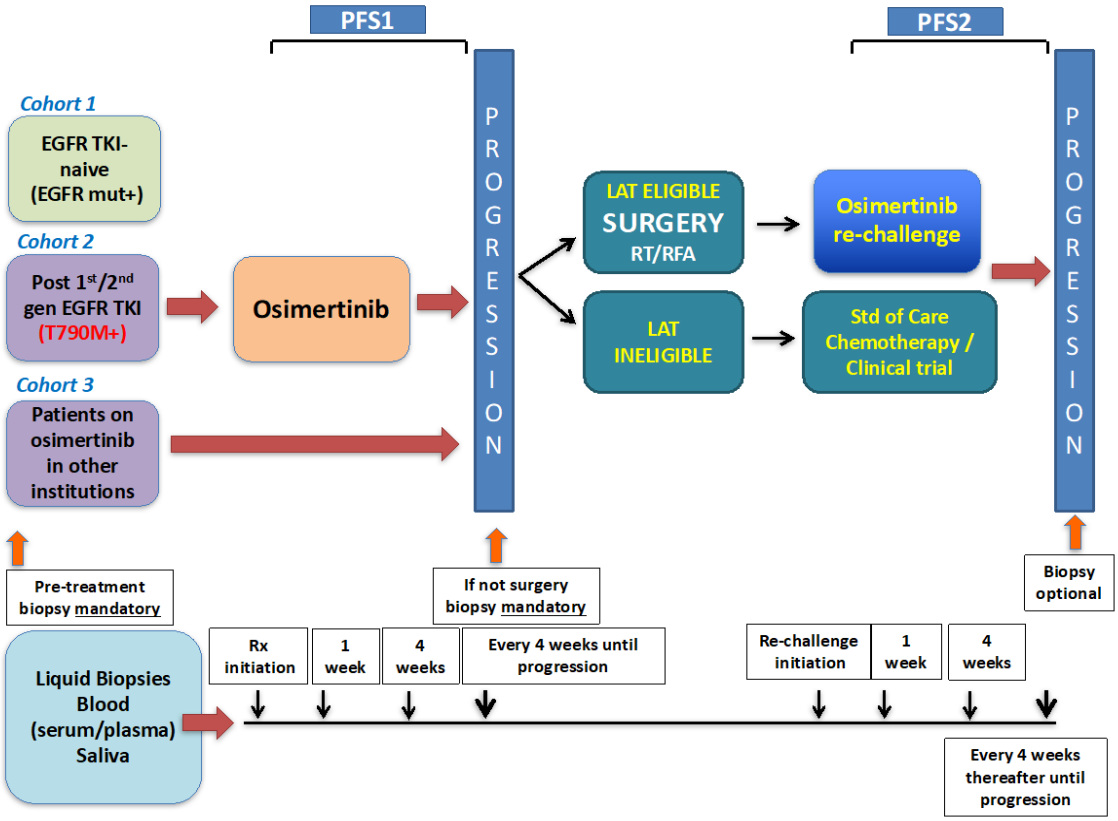
- Histologically confirmed advanced lung adenocarcinoma with EGFR-sensitizing somatic mutations or a germline T790M mutation and no prior EGFR tyrosine kinase inhibitor (TKI) therapy (Cohort 1); OR progressive disease after 1st or 2nd generation EGFR TKI therapy harboring somatic T790M mutation (Cohort 2); or patients with progressive disease after treatment with osimertinib who are eligible for local ablative therapy (Cohort 3). If biopsy for EGFR mutation status confirmation is not clinically feasible, EGFR mutations may be confirmed by ctDNA analysis using a CLIA certified assay.
- Presence of measurable disease per RECIST version 1.1
- ECOG performance status 0-2
- Adequate end organ function
- If patients are not eligible for LAT, they will be referred for standard of care chemotherapy as per treating physicians' discretion. These patients may also be considered for other clinical trials.

Design:

- This is a single-institution, open-label phase II trial of osimertinib.

- Eligible patients not previously treated with osimertinib will be treated with osimertinib daily until disease progression. At the time of progression, patients with oligoprogressive disease (no more than 5 sites of progressive disease) will be assessed for LAT.
- If patients are eligible for LAT, osimertinib will be resumed after LAT and they will be followed for second progression on osimertinib (PFS2).
- If patients progress at the same site where LAT has been performed before, the progression will be considered to be a result of inadequate ablation and they will be considered for repeat LAT and again re-challenged with osimertinib if clinically feasible.
- Tumor samples will be obtained at baseline by a mandatory biopsy. At the time of first progression on osimertinib if a patient is eligible for surgery as a form of LAT, then a tissue sample will be obtained for genomic and proteomic studies to identify mechanisms of acquired resistance. For patients who are not eligible for LAT or a form of LAT that is not surgery (radiation, radiofrequency ablation, cryoablation), then a mandatory biopsy will be performed, if clinically safe, to obtain tissue for above studies.
- Re-treatment will be allowed for a small number of subjects.

SCHEMA



Eligibility for local ablative therapy (LAT) is based on the following criteria:

a. Oligoprogressive disease – no more than 5 sites of progressive disease that are amenable to treatment with LAT (surgery, radiation therapy, radiofrequency ablation, or cryoablation) independent of size and location of lesions.

b. Patients with neurological or imaging signs of leptomeningeal disease and/or confirmed by a lumbar puncture occurring after initiation of osimertinib will be considered for LAT if radiation or intrathecal methotrexate can be administered for local treatment.

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1.1.1.2 Assess mechanisms of acquired resistance to osimertinib

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1.2 BACKGROUND AND RATIONALE

1.2.1 NSCLC

Overview of NSCLC

Lung cancer is the leading cause of cancer deaths for both men and women in the United States and worldwide. 159,260 patients died of lung cancer in the United States in 2014, 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], which is not amenable to curative treatment.

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].

Targeted therapy for advanced NSCLC

In the past decade, insights into the genetic and molecular pathogenesis of lung cancer have led to the development of targeted therapies. Erlotinib is an orally active reversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which has demonstrated marked clinical efficacy over standard chemotherapy in *EGFR* mutation-positive advanced NSCLC[10]. *EGFR* mutations are the most frequent genetic abnormalities observed in NSCLC, especially in adenocarcinoma subtype[11]. The most predominant *EGFR* mutations are in-frame deletions in exon 19 and L858R missense mutation[11], and the majority of patients whose tumor harbors these mutations are highly sensitive to EGFR-TKIs. Several 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]. The median PFS 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].

Gefitinib is another first-generation orally administered EGFR-TKI. Randomized trials that compared gefitinib with standard chemotherapy for the treatment of advanced NSCLC with *EGFR* mutations in the first-line setting showed objective response rates of 62-74% for gefitinib, and 31-32% for chemotherapy[16, 17]. Patients who were treated with gefitinib had a prolonged progression-free survival (9.2-10.8 months), as compared with those who were treated with standard chemotherapy (5.4-6.3 months). Like erlotinib, most adverse events associated with gefitinib were grade 1 or 2. The most common adverse reactions of gefitinib included skin reactions, transaminitis, and diarrhea. Gefitinib was approved by the FDA for the first-line treatment of patients with advanced *EGFR* mutation-positive NSCLC in 2015[18].

Afatinib is a selective, irreversible, orally bioavailable second-generation EGFR-TKI that was approved by the FDA in 2013[19]. In a phase III study of 345 patients with metastatic NSCLC harboring *EGFR* mutations, 230 and 115 were randomized to afatinib and cisplatin/pemetrexed, respectively[20]. The median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR]=0.58; 95% CI=0.43 to 0.78; p=0.001). In patients whose tumors carry exon 19 deletions or L858R, the median PFS was 13.6 months for afatinib and 6.9 months for chemotherapy. In a pooled analysis of two randomized trials (LUX-Lung 3 and LUX-Lung 6), afatinib was shown to improve overall survival in patients whose tumors harbor exon 19 deletions[21]. The most frequent adverse events from afatinib were diarrhea, rash/acne, stomatitis, and decreased appetite[20].

Resistance to EGFR-TKI

Resistance to single-agent targeted therapies is virtually unavoidable in metastatic carcinomas[22], and it poses a major challenge to the treating physician. Although first and second-generation EGFR-TKIs produce remarkable clinical responses, 5-10% of patients with *EGFR* mutation-positive NSCLC are refractory to EGFR-TKIs, and up to 40% of patients harboring *EGFR* sensitizing mutations do not attain a major response to the first-generation EGFR-TKIs (erlotinib and gefitinib)[4, 5, 16, 17], indicating the existence of intrinsic resistance mechanisms. Moreover, even those who achieved an objective response invariably develop acquired resistance. Largely, resistance mechanisms to targeted therapy involve alterations in the gene that encodes the target of targeted agent and activation of alternative signaling pathways[23]. *KRAS* mutation, Cripto1 overexpression, *MET* gene amplification, and HGF overexpression have been implicated in the molecular pathogenesis of intrinsic resistance to EGFR-TKIs[24-26]. Known acquired mechanisms of resistance to EGFR-TKIs include *EGFR* T790M mutation (50-60%), and less frequently *MET* gene amplification, hepatocyte growth factor (HGF) overexpression, mutations in the *PIK3CA* gene, epithelial to mesenchymal transition, and small cell lung cancer transformation[25, 27-31].

1.2.2 Osimertinib

Non-clinical studies of Osimertinib

Osimertinib is an irreversible, potent, and selective third-generation EGFR-TKI that targets both sensitizing and T790M *EGFR* mutations[32]. 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[32]. 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[32]. 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.

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-TKI[33]. 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 cohort, daily dosing of osimertinib was initiated immediately.

A total of 253 patients from 33 sites were enrolled in the study[33]. 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)[33]. 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 (9.6 months in *EGFR* T790M-positive patients, 2.8 months in EGFR T790M-negative patients). 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. 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[34].

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)[35]. 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.

It has been shown that osimertinib has excellent penetration of the mouse blood-brain barrier compared to other EGFR-TKIs including gefitinib, rociletinib, or afatinib[36]. Osimertinib also showed activity against brain metastases from *EGFR*-mutated NSCLC in early clinical reports[36]. At the 2016 ASCO annual meeting, results from a phase I study of osimertinib for patients with leptomeningeal disease (NCT02228369) were presented[37]. Patients were eligible if they had progressed on prior EGFR-TKI therapy and leptomeningeal disease is confirmed by positive cerebrospinal fluid cytology. Patients were treated with osimertinib 160 mg once daily. Of 12 patients who were treated >3 weeks and reached a 12-week intracranial IC imaging assessment, 7 had radiological improvement, 2 had stable disease, and 3 were not evaluable, indicating activity of osimertinib in patients with leptomeningeal disease. The most common treatment-associated side effects were skin rash (n=15; 11 grade 1, 4 grade 2) and diarrhea (n=8; 5 grade 1, and 3 grade 2). In one patient, grade 3 neutropenia was observed, but the patient recovered to grade 2 after a dose interruption and resumed osimertinib at 80 mg once daily.

1.2.3 Treatment options after progression on EGFR-TKI

Several clinical factors such as symptoms and disease burden need to be taken into account when choosing the best treatment option for patients who developed resistance to first-line EGFR-TKI targeted therapy[38]. For patients who have disease progression based on the Response Evaluation Criteria in Solid Tumors (RECIST) and yet remain asymptomatic, the use of erlotinib beyond progression was associated with a delay in initiation of chemotherapy[39] and thus constitutes a reasonable option. Another line of evidence supporting this approach derives from previous observations that some patients experience a disease flare leading to hospitalization or death after discontinuation of erlotinib or gefitinib[40].

In general, outside clinical trials, systemic chemotherapy is recommended for patients who have symptomatic disease progression, especially if there are multiple progressive lesions[41, 42]. However, treatment outcomes associated with second-line chemotherapy are modest; the median PFS after second-line chemotherapy for patients who progressed on EGFR-TKI therapy is only 4-5 months[41, 43, 44]. Continuation of EGFR-TKI therapy beyond progression in addition to commencement of chemotherapy has not been shown to improve clinical outcomes. A randomized phase II study that compared chemotherapy (pemetrexed or docetaxel) with chemotherapy plus erlotinib in patients with progressive NSCLC following prior benefit from erlotinib demonstrated that continuation of erlotinib was associated with a significant increase in toxicities, but not with improvement in treatment outcomes[43]. In a phase III trial of 265 patients with advanced NSCLC who progressed on first-line gefitinib, addition of gefitinib to platinum-based doublet chemotherapy did not prolong PFS[41]. The use of afatinib beyond progression was evaluated in a

phase III study that involved 202 patients who progressed on erlotinib/gefitinib and afatinib[44]. Study participants were randomized 2:1 to afatinib plus paclitaxel or single-agent chemotherapy of investigator's choice. Although preliminary data showed that there was a significant improvement in PFS favoring continuation of afatinib (median 5.6 vs. 2.8 months, hazard ratio=0.60, p=0.003), study data are not mature yet. For patients who developed the *EGFR* T790M mutation after first-line EGFR-TKI, osimertinib is a treatment option. However, about half of patients with acquired resistance to first- or second-generation EGFR-TKI would not benefit from osimertinib. Moreover, it is almost certain that selection pressure will lead to the emergence of newer clones that are resistant to treatment with osimertinib. In fact, a newly identified EGFR mutation (C797S) that results in acquired resistance to osimertinib has been reported recently[45].

Because targeted therapies are highly active in molecularly selected patients with NSCLC and generally better tolerated than chemotherapy, patients would benefit from continuation of a TKI and delay in initiation of subsequent therapy such as chemotherapy. Therefore various strategies need to be evaluated to delay a switch in systemic therapy due to emergence of acquired resistance to EGFR TKI therapy. In this regard, exploring the role of local therapies for patients with metastatic NSCLC who progressed on EGFR-TKI therapy merits further investigation. There are several theoretical benefits of using local therapies for advanced NSCLC. First, local progression is the predominant pattern of failure for patients with advanced NSCLC treated with first-line systemic therapy[46]; among patients seen at the University of Colorado between 2005 and 2008, the pattern of failure analysis demonstrated that the first site of extracranial progression was local only in 64% of patients[47]. Second, the Norton-Simon hypothesis suggests that the effect of systemic therapy is proportional to the rate of tumor growth at the time of treatment and tumor growth follows a sigmoidal pattern[48, 49]. Local ablative therapy may move the tumor growth curve back to a state of exponential growth and thereby augment the antitumor activity of systemic therapy[46]. Third, local therapy may serve as a means of eliminating an evolutionary reservoir of resistant subclones[50] and thus help extend the use of targeted therapy.

While local therapies such as surgery, stereotactic radiation therapy, and radiofrequency ablation have been shown to be effective for several types of cancer including colorectal cancer, sarcoma, and renal cell carcinoma in the metastatic disease setting[51], the role of local therapies for the treatment of NSCLC with limited metastatic disease is not defined yet and available data are largely from retrospective case series studies or subgroup analyses of larger prospective studies[52-55]. Findings from these studies, however, indicate that there might be a subset of patients who benefit from aggressive local therapy (**Table 1**). The therapeutic utility of combining local ablative therapy and targeted therapy for the treatment of oligometastatic NSCLC was recently examined. In a single-arm phase II study, 24 patients with metastatic NSCLC and no more than 6 sites of extracranial disease who progressed through previous platinum-based chemotherapy were treated with stereotactic body radiation therapy (SBRT) combined with erlotinib[56]. Of the 13 patients tested for *EGFR* mutations, no one was found to have activating *EGFR* mutations. This study showed that the combination of SBRT and erlotinib was well tolerated. The median PFS and overall survival were 14.7 months and 20.4 months, respectively. There results were superior to those from historical controls treated only with systemic chemotherapy, although it must be acknowledged that making a comparison to a historical control does not account for differences in patient populations or other confounding factors.

To the best of our knowledge, there are two studies that have examined the efficacy of local ablative therapy with continued targeted therapy in patients with acquired resistance to EGFR-TKIs. In a retrospective study of 184 patients who have documented progression on erlotinib or

gefitinib, 18 patients were treated with one or more local therapies, excluding intracranial treatments, for progressive *EGFR* mutation-positive NSCLCs[57]. The most common site of metastatic disease was lung, followed by lymph node, bone, and brain in the local therapy group, and all patients except one patient had oligometastatic disease, defined as less than 5 sites of disease. Local therapies consisted of metastasectomy (lobectomy, wedge resection, pneumonectomy, adrenalectomy), radiofrequency ablation (RFA), and stereotactic radiotherapy. Most local therapies were well tolerated, with 85% of patients restarting EGFR-TKI therapy within 1 month of local therapy. The median time to progression after local therapy was 10 months (range 1 to 51 months), and the median time from local therapy until a change in systemic therapy was 22 months (range 1 to 54 months). The median overall survival from local therapy was 41 months (range 1 to >65 months). Another single-center study that assessed the benefits of the combination of local therapy and continued TKI therapy (crizotinib or erlotinib) in patients with oligoprogressive disease, defined as nonleptomeningeal CNS and/or 4 or fewer of extracranial progression[58]. 15 of 28 patients (54%) treated with crizotinib and 10 of 23 patients (43%) treated with erlotinib were deemed suitable for local therapies involving surgery or radiation. Among the 25 patients treated with local therapy and continued TKI therapy, 10 first progressed in the central nervous system (CNS) and 15 had disease progression in extracranial sites with the most common sites being lung and bone. Patients with less than four CNS metastases received stereotactic radiosurgery (SRS), and those with more than four CNS metastatic lesions were treated with whole brain radiation therapy (WBRT). Most of the 15 patients who had extracranial disease progression received SBRT, with 8 of 15 (53%) having a single site of progression ablated. One patient underwent adrenalectomy. The subsequent median progression-free survival from the time of first progression (PFS2) was 7.1 months for patients with initial CNS only progression. The median PFS2 for patients with initial extracranial progression was 4.0 months. The majority of adverse events in this case-series occurred in patients who received WBRT. Grade 1/2 fatigue, nausea, and anorexia were the most common side effects related to radiation therapy other than WBRT. These data indicate that the use of local therapies was safe and feasible in patients who acquired resistance to EGFR-TKIs, and may have a role in extending the duration of clinical benefit from targeted therapies.

Based on these observations, we propose a phase II trial to explore the role of local ablative therapy after emergence of resistance to osimertinib in patients with oligoprogressive *EGFR* mutation-positive NSCLC. Another important goal of this study is to study the mechanisms of resistance to osimertinib. Patients with *EGFR* mutation-positive NSCLC who are treatment-naïve or who progressed after EGFR-TKI therapy and acquired the T790M mutation will be eligible for the trial. The advantage of using osimertinib in the first-line treatment setting 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 other approved EGFR-TKIs.

Table 1. Selected Clinical Trials of Local Ablative Therapy for Pulmonary

Oligoprogressive/Oligometastatic NSCLC

Reference (Publication year)	Study population	Study design	No. of Patients	Median Follow-up (months)	Previous lines of systemic therapy	Site of metastatic disease	Types of procedures (1: Surgery, 2: Radiation, 3: Radiofrequency ablation)	Primary Endpoint	
Weickhardt et al. (2012)(58)	Oligoprogressive metastatic NSCLC with acquired resistance to EGFR-TKI or crizotinib	Retrospective	25	NA	2.5	Adrenal, bone, liver, lung, lymph node	1, 2	PFS1=9.8 months, PFS2=6.2 months, median OS data not mature at the time of analysis	
Yu et al. (2013)(57)	Oligoprogressive metastatic NSCLC with acquired resistance to EGFR-TKI	Retrospective	18	NA	NA	Bone, brain, lung, lymph node, visceral	1, 2, 3	PFS1=19 months, PFS2=10 months, median OS from local therapy=41 months	
Porte et al. (2001)(59)	Oligometastatic NSCLC with a solitary adrenal metastasis	Retrospective	43	23.8	NA	Adrenal	1	Median PFS=13 months, median OS=11 months	3 patients survived more than 5 years
Holy et al. (2011)(60)	Oligometastatic NSCLC with adrenal metastases	Retrospective	18	21	NA	Adrenal	2	Median PFS=4.2 months, median OS=23 months	PFS was longer (12 months) in 13 patients with a solitary adrenal metastasis
Luketich et al. (1996)(61)	Oligometastatic NSCLC with a solitary adrenal metastasis	Retrospective	8	NA	NA	Adrenal	1	Median OS=33 months	Median OS in patients treated with medical therapy only was 8.5 months.
Patchell et al. (1990)(62)	Advanced solid tumors with a single metastasis to the brain	Randomized	48 (37 patients with NSCLC)	7	NA	Brain	1, 2 (surgery plus radiation vs. radiation only)	Median OS=10 months in the surgery plus radiation vs. 3.8 months in the radiation group; P<0.01	Patients in the surgery group maintained Karnofsky score much longer.

Reference (Publication year)	Study population	Study design	No. of Patients	Median Follow-up (months)	Previous lines of systemic therapy	Site of metastatic disease	Types of procedures (1: Surgery, 2: Radiation, 3: Radiofrequency ablation)	Primary Endpoint	
Andrews et al. (2004)[63]	Advanced solid tumors with one to three brain metastases	Randomized	331 (211 patients with NSCLC)	NA	NA	Brain	2 (stereotactic radiosurgery plus WBRT vs. WBRT)	Median OS=6.5 months in the stereotactic radiosurgery group vs. 4.9 months in the WBRT only group (p=0.04)	A statistically significant improvement in performance status in the stereotactic radiosurgery group
Furak et al. (2005)[64]	Oligometastatic NSCLC with brain metastases	Retrospective	65	NA	NA	Brain	1	Median OS=19 months for synchronous patients, 12 months for metachronous patients	
Burt et al. (1992)[65]	Oligometastatic NSCLC with brain metastases	Retrospective	185	NA	NA	Brain	1	Median OS=14 months	10-year survival=7%
De Ruysscher et la. (2012)[66]	Oligometastatic NSCLC	Prospective	39	27.7	NA	Adrenal, bone, brain, liver, lung, lymph node, muscle, ovary, pleura	1, 2	Median PFS=12.1 months, median OS=13.5 months	
Khan et al. (2006)[52]	Oligometastatic NSCLC	Retrospective	23	17	NA	Adrenal, bone, brain, intrapulmonary, lymph node, soft tissue	1, 2	Median OS=20 months	

WBRT: whole brain radiation therapy

PFS: Progress-free survival

OS: Overall survival

PFS1: Time from initiation of targeted therapy to first progression of disease or clinical progression, or death from any cause

PFS2: Time from the first progression until second progression on the same targeted therapy

1.2.4 Rationale

1.2.4.1 Rationale for study design, doses and control groups

This is a single-institution, open-label phase II trial. This study aims to assess the role of local ablative therapy in the treatment of patients with *EGFR* mutation-positive NSCLC after oligoprogression on osimertinib. Oligoprogression is defined as no more than 5 sites of progressive disease that are amenable to treatment with LAT (surgery, radiation therapy, radiofrequency ablation, or cryoablation) independent of size and location of lesions. There is no FDA-approved treatment for patients who progressed on osimertinib and thus assessing the

efficacy of local ablative therapy as a strategy to extend the benefits of osimertinib merits further investigation.

In the phase 1 dose escalation study of osimertinib (D5160C00001, AURA), once daily doses of 20, 40, 80, 160, and 240 mg of osimertinib were evaluated. Based on the totality of the safety, pharmacokinetic and preliminary efficacy data, 80 mg once daily was selected as the recommended phase II dose. In light of these data, the starting dose of osimertinib will be 80 mg per day for patients without leptomeningeal disease. For patients with leptomeningeal disease, the start dose of osimertinib will be 160 mg per day based on the results of the BLOOM trial (NCT02228369). Patients may continue to receive osimertinib as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria. No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status.

Patients who progress on their initial treatment with osimertinib and receive LAT therapy (surgery, radiation therapy, or RFA) followed by osimertinib will be evaluated for their time to second progression (PFS2). The objective will be to estimate the PFS2 for these patients and also to determine if the PFS2 result may be potentially superior to that of historic controls. 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[67].

Another important goal of this study is to assess mechanisms of acquired resistance to osimertinib. Tumor samples will be obtained prior to initiation of treatment and upon development of acquired resistance. Whole exome, transcriptome and/or whole genome sequencing and proteomics analyses will be performed on the tumor samples. In addition, this protocol will involve longitudinal acquisition of liquid biopsies (blood, saliva, urine), which will be used for comprehensive proteogenomic analysis. Germline DNA will be extracted from peripheral blood and the information will only be used for the identification of somatic variants. Leftover biological samples will be frozen and stored in Dr. Figg's lab.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

For inclusion in the study subjects should fulfill the following criteria:

2.1.1.1 Provision of informed consent prior to any study specific procedures

2.1.1.2 Patients *(male/female)* must be ≥ 18 years of age.

2.1.1.3 Patients with histologically confirmed, by the NCI Laboratory of Pathology or by CLIA-certified Next Generation Sequencing or cobas® EGFR Mutation Test v1/2 at an outside institution, advanced lung adenocarcinoma with EGFR-sensitizing somatic mutations or a germline T790M mutation (detected histologically or via ctDNA analysis using a CLIA assay) with:

2.1.1.3.1 No prior EGFR tyrosine kinase inhibitor (TKI) therapy (Cohort 1)

OR

2.1.1.3.2 Progressive disease after 1st or 2nd generation EGFR TKI therapy harboring somatic

T790M mutation (Cohort 2)

OR

2.1.1.3.3 Progressive disease after treatment with osimertinib who are eligible for local ablative therapy (Cohort 3)

2.1.1.4 Presence of measurable disease per RECIST version 1.1. See Section **6.3.2** for the evaluation of measurable disease.

2.1.1.5 In patients with suspected leptomeningeal disease, the diagnosis of leptomeningeal disease should be confirmed by the presence of neurological or imaging signs and/or positive CSF cytology.

2.1.1.6 ECOG performance status 0-2. (See **Appendix A**)

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

2.1.1.8 Females should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

2.1.1.8.1 Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments

2.1.1.8.2 Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution

2.1.1.8.3 Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

2.1.1.9 Females of child-bearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing osimertinib. Acceptable methods of contraception include total and true sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (IUS Levonorgestrel Intra Uterine System (Mirena), Medroxyprogesterone injections (Depo-Provera), copper-banded intra-uterine devices, and vasectomized partner. All hormonal methods of contraception should be used in combination with the use of a condom by their male sexual partner for intercourse.

2.1.1.10 Male patients should be willing to use barrier contraception. Male patients should be asked to use barrier contraceptives (i.e., by use of condoms) during sex with all of their female partners during the trial and for a washout period of 3 months. Patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing osimertinib treatment. If male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of osimertinib treatment.

2.1.1.11 Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

2.1.2 Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

2.1.2.1 Any unresolved toxicities from prior therapy greater than Common Terminology Criteria

for Adverse Events (CTCAE) grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy.

2.1.2.2 Treatment with an investigational drug within five half-lives of the compound.

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

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

2.1.2.5 Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors of CYP3A4 (at least 1 week prior) and potent inducers of CYP3A4 (at least 3 week prior) (**Appendix B**) will only be eligible at the PI's discretion.

2.1.2.6 Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.

2.1.2.7 Patients with CNS metastases who are neurologically unstable.

2.1.2.8 Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD

2.1.2.9 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

2.1.2.9.1 Absolute neutrophil count <1 x 10^9/L

2.1.2.9.2 Platelet count <100 x 10^9/L

2.1.2.9.3 Hemoglobin <90 g/L

2.1.2.9.4 Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases

2.1.2.9.5 Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases

2.1.2.9.6 Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases

2.1.2.9.7 Creatinine >1.5 times ULN concurrent with creatinine clearance <30 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN

2.1.2.10 Any of the following cardiac criteria:

2.1.2.10.1 Resting corrected QT interval (QTc using Fredericia's formula) > 480 msec

2.1.2.10.2 Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block)

2.1.2.10.3 Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT

syndrome or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medication known to prolong the QT interval

2.1.2.11.4 Significant symptomatic congestive heart failure, per PI judgement

2.1.2.11 Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib

2.1.2.12 History of hypersensitivity to osimertinib (or drugs with a similar chemical structure or class to osimertinib) or any excipients of these agents

2.1.2.13 Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements

2.2 RECRUITMENT

Trial information will be posted on NIH websites accessible to the public such as ClinicalTrials.gov and NIH social media forums. Patients will also be recruited from the patients seen in the TGMB clinic.

2.2.1 Inclusion of Women and Minorities

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

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	8	+	8	=	16
Not Hispanic or Latino	42	+	42	=	84
Ethnic Category: Total of all subjects	50	+	50	=	100
Racial Category					
American Indian or Alaskan Native	2	+	2	=	4
Asian	15	+	15	=	30
Black or African American	5	+	5	=	10
Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	27	+	27	=	54

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Racial Category: Total of all subjects	50	+	50	=	100
Accrual Rate: 2 patients/month	**Total Expected Accrual**: 100				

2.3 SCREENING EVALUATION

Procedures will be performed according to the **Study Calendar**. At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study. All subjects will be required to provide consent for a mandatory tumor biopsy for entry into this study. This consent is included in the main subject informed consent form. All screening procedures must be performed within 4 weeks (28days) prior to starting osimertinib unless otherwise stated. The screening procedures include:

- Complete history and physical examination including vital signs, height, weight and ECOG performance score (see **Appendix A**).
- Imaging studies: Patients should have a radiographical evaluation with contrast-enhanced CT scan of the chest/abdomen/pelvis. Whole-body FDG-PET scan may be done at the investigator's discretion. Brain imaging will also be obtained via either MRI or CT of the brain with contrast.
- Electrocardiogram (ECG)
- Echocardiogram
- Confirmation of diagnosis and mutation status by the NCI Laboratory of Pathology, or as follows:
  Patients whose EGFR mutation status was confirmed by CLIA-certified Next Generation Sequencing or cobas® EGFR Mutation Test v1/2 at an outside institution may forego confirmation of EGFR mutation status at the NCI before enrolling into the protocol. EGFR mutations detected in ctDNA by CLIA assay are acceptable for enrollment. If tumor tissue from the mandatory biopsy is available and the quality of the sample is adequate for further testing, it will be tested for the presence of EGFR mutations (included in the cancer gene mutation panel), or by whole exome sequencing (WES) under Clinomics to confirm *EGFR* mutation status. In case EGFR mutation is not detected at the NCI, the test will be repeated by the Laboratory of Pathology, and if EGFR mutation is still not detected, study investigators will determine whether or not to keep the patient on the protocol based on the patient's clinical symptoms and an objective response evaluation at the first tumor imaging in 8 weeks.

A block of primary tissue (or 15-20 unstained sections on charged slides) from the time of diagnosis and/or the latest biopsy at progression will be required from each patient. Referring institutions will send the tumor block or 15-20 unstained sections on charged slides to CCR/NCI for confirmation of diagnosis and mutation status. If adequate tissue is not available, a fresh biopsy will be performed that will also be a part of the baseline mandatory biopsy if patient is eligible and signs consent to this protocol. In case a biopsy at study entry is not clinically safe and biopsy

material from a previously performed procedure is available, archival tissue will be obtained for mutation testing required to determine eligibility for this protocol. ctDNA analysis for EGFR mutation detection may also be considered in patients where biopsy is not clinically feasible.

- Laboratory evaluation (baseline tests to be obtained within one week prior to starting treatment unless otherwise indicated)
    - 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 (ALP), lactate dehydrogenase (LDH), bilirubin, albumin, creatinine kinase.
    - Baseline glomerular filtration rate (GFR) calculation.
    - Serum or urine beta-hCG for female patients of childbearing potential within 72 hours prior to starting treatment.
- Cerebrospinal fluid analysis (cytology, cell counts, and protein and glucose levels) will be performed only in patients with suspected leptomeningeal disease.

NOTE: An ophthalmologic evaluation will also be performed during the screening period, but it is not an exclusion criterion. See Section **6.4.4**.

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols).

2.4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4.1 Treatment Assignment and Randomization/Stratification Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Oligoprogressive EGFR-Mutated NSCLC EGFR TKI-naïve (EGFR mutation +)
2	Cohort 2	Oligoprogressive EGFR-Mutated NSCLC post 1st/2nd gen EGFR TKI (T790M+)

3	Cohort 3	Oligoprogressive EGFR-Mutated NSCLC; pts treated with osimertinib in other institutions and developed acquired resistance

Arms

Number	Name	Description
1	Arm 1	Osimertinib followed by LAT followed by osimertinib
2	Arm 2	LAT followed by osimertinib

Stratifications

Stratification is not applicable to this study.

Randomization and Arm Assignment

Randomization is not applicable to this study. Subjects in Cohorts 1 and 2 will be directly assigned to Arm 1. Subjects in Cohort 3 will be directly assigned to Arm 2.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a single-institution, open-label phase II trial. Patients with *EGFR* mutation-positive NSCLC who are treatment-naïve (cohort 1) or who progressed on first- or second-generation EGFR-TKIs – erlotinib, gefitinib, afatinib – and acquired the T790M mutation (cohort 2) will be included in the study and treated with osimertinib. These groups of patients will be followed for progression-free survival (PFS1). At the time of progression, their candidacy for local ablative therapy will be assessed at a multidisciplinary conference. Eligibility for local ablative therapy (LAT) is based on the following criteria:

1. Oligoprogressive disease – no more than 5 sites of progressive disease that are amenable to treatment with LAT (surgery, radiation therapy, radiofrequency ablation, or cryoablation) independent of size and location of lesions.
2. Patients with neurological or imaging signs of leptomeningeal disease and/or confirmed by a lumbar puncture occurring after initiation of osimertinib will be considered for LAT if radiation or intrathecal methotrexate can be administered for local treatment. In these cases, following LAT, osimertinib will be increased to 160 mg dose. The dose of osimertinib for leptomeningeal disease treatment under this protocol is 160 mg of osimertinib. Osimertinib has superior penetration of the blood brain barrier and the 160 mg dose has been used extensively in clinical studies with minimal side effects.

If patients are eligible for local ablative therapy, osimertinib will be resumed at the discretion of the PI once the patient has completed LAT. They will be followed for second progression on osimertinib (PFS2). If patients are not eligible for local ablative therapy, they will be referred for standard of care chemotherapy as per treating physicians' discretion. These patients may also be considered for other clinical trials.

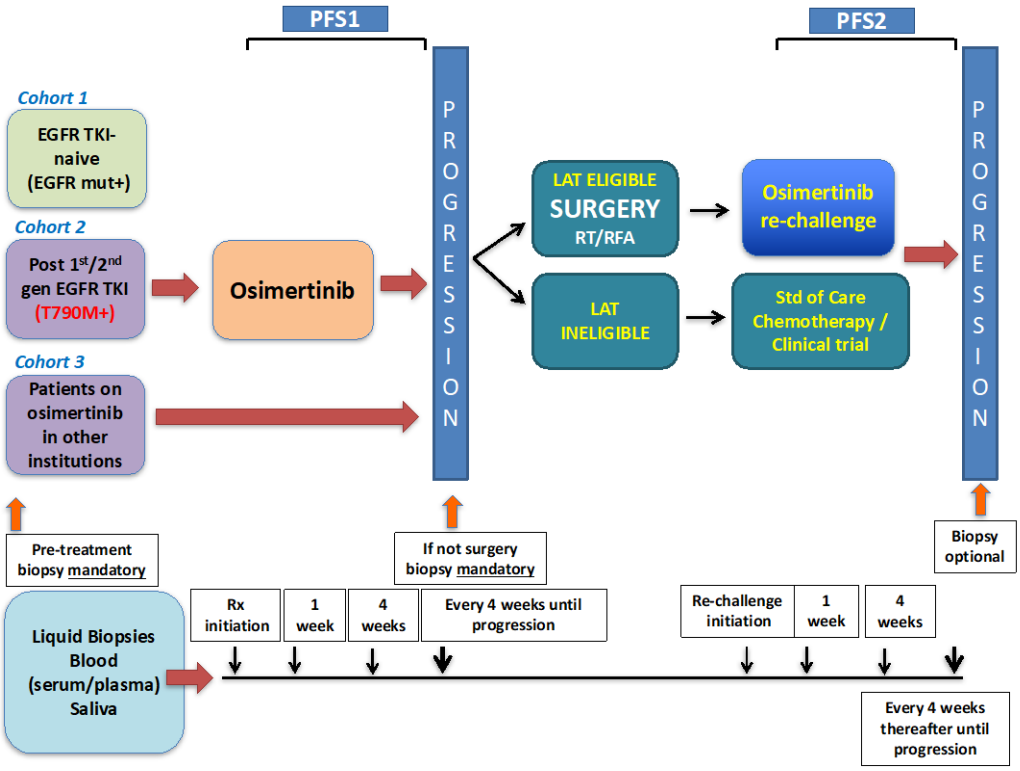
Those who were treated with osimertinib in other institutions in on-going clinical trials and developed acquired resistance (cohort 3) will also be assessed for their candidacy for local ablative therapy and may be enrolled onto the study if they are eligible for local ablative therapy. These patients will only be part of the LAT and re-challenge with osimertinib part of the study.

Tumor samples will be obtained at baseline by a mandatory biopsy unless fresh tissue was collected at screening. At the time of first progression on osimertinib if a patient is eligible for surgery as a form of LAT, then tissue sample will be obtained for all correlative studies. For patients who are not eligible for LAT or a form of LAT that is not surgery (radiation, radiofrequency ablation, cryoablation), then a mandatory biopsy will be performed, if clinically safe, to obtain tissue for correlative studies. If a biopsy at this time is not clinically safe, then tissue obtained from the previous biopsy for mutation testing needed for eligibility for this protocol may be used. At the time of second progression on osimertinib, a fresh tumor biopsy is optional.

3.2 RE-TREATMENT OF SUBJECTS

A small number of subjects may be eligible for re-treatment and would be required to meet all eligibility criteria at the time of re-treatment. We do not anticipate changes in the risk profile at the time of initial enrollment versus re-treatment.

Patients who were initially thought to have progression by RECIST criteria, and hence taken off therapy, and were later found to have a biopsy-proven alternative diagnosis such as pneumonia or inflammation may be eligible for re-treatment on the study. In such cases, interruption of osimertinib should not be more than one month.



3.3 DRUG ADMINISTRATION

Treatment will be administered on an outpatient basis. Courses are defined as 28 days of dosing. The starting dose of osimertinib will be 80 mg per day for patients without leptomeningeal disease and 160 mg per day for those with leptomeningeal disease at baseline. Please see section **13.1.3** for detailed drug administration instructions. There is no limit to the number of cycles a patient can receive. In the event of an adverse event at least possibly related to the agent, the dose of osimertinib should be adjusted according to the guidelines in Section **3.7**. Reported adverse events and potential risks are described in Section **13**.

Patients will be requested to maintain a medication diary (See **Appendix C**) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. The protocol will follow NIH policy for *Conducting and Documenting Drug Accountability for Oral Investigational Agents that are Self-Administered by Patients*.

3.4 DOSING DELAYS/DOSE MODIFICATIONS

3.4.1 Management of IP related toxicities

Dose adjustment for adverse events should be in accordance with the following table:

Table 2. Osimertinib dose adjustment information for adverse reactions

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue osimertinib
Cardiac	QTc interval greater than 500 msec	Withhold osimertinib. If QTc interval recovers less than 481

Target Organ	Adverse Reaction[a]	Dose Modification
	on at least 2 separate ECGs	msec within 4 weeks, then restart at one dose level lower. If not resolved after 4 weeks, then the patient should be withdrawn from study therapy. If there is further increase of QTc greater than 500 msec at the lowest dose level, permanently discontinue osimertinib.
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue osimertinib
	Asymptomatic, absolute decrease in LVEF of 10% from baseline	Withhold osimertinib for up to 4 weeks. If resolved to baseline LVEF, resume. If not improved to baseline, permanently discontinue.
	Symptomatic congestive heart failure	Permanently discontinue osimertinib
Other	Grade 3 or higher adverse reaction, unless in the opinion of the PI the patient can safely continue	Withhold osimertinib for up to 4 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 4 weeks	Osimertinib may be restarted at the same dose or a lower dose per investigator discretion.
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 4weeks	Permanently discontinue osimertinib

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

If a patient experiences a CTCAE grade 3 or higher and/or unacceptable toxicity (any grade), where the clinician considers the event of concern to be specifically associated with osimertinib (and not attributable to the disease or disease-related processes for which patient is being treated), dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Once a patient has a dose reduction due to toxicity, the dose will not be re-escalated. Only one dose reduction will be allowed per patient except for patients with leptomeningeal disease at baseline who started osimertinib at 160 mg per day (two dose reductions are allowed in those with leptomeningeal disease at baseline). Occurrence of an event requiring dose reduction at the 40 mg dose will result in removal from study therapy.

If the toxicity resolves or reverts to ≤CTCAE grade 2 within 4 weeks of onset, treatment with osimertinib may be restarted at the same dose or a lower dose using the rules below for dose modifications (**Table 3**). There will be no individual modifications to dosing schedule in response

to toxicity, only potential dose reduction or dose interruption.

If the toxicity does not resolve to ≤CTCAE grade 2 after 4 weeks, (then the patient should be withdrawn from study therapy and observed until resolution of the toxicity.

Table 3. Dose Interventions

Intervention	Osimertinib Dose
Starting Dose*	80 mg daily
Reduced Dose	40 mg daily

* The starting dose for patients with leptomeningeal disease at baseline is 160 mg daily. Two dose reductions to 80 mg daily and 40 mg daily are allowed in these patients.

On resolution of toxicity within 4 weeks:

If an event subsequently requires dose interruption, osimertinib may restart at the same dose or the reduced dose, on resolution/improvement of the event at the discretion of the clinician.

3.4.1.1 Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of interstitial lung disease is observed, an interruption in osimertinib dosing is recommended. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage.

In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study drug should be permanently discontinued. Where ILD is suspected, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper.

In the absence of a diagnosis of interstitial lung disease, osimertinib may be restarted.

3.4.1.2 QTc Prolongation

Patients with QTcF prolongation fulfilling the following criteria (i.e., confirmed QTcF prolongation to > 500 msec should have osimertinib interrupted and regular ECGs performed until QTc interval is less than 481 msec. If QTc interval recovers to less than 481 msec within 4 weeks, then restart at a reduced dose (40 mg). If not resolved after 4 weeks, then the patient should be withdrawn from study therapy. If there is further increase of QTc greater than 500 msec at 40 mg dose, permanently discontinue osimertinib.

3.4.1.3 Corneal Ulceration

Patients experiencing corneal ulceration will not be permitted to restart osimertinib treatment.

3.4.1.4 Skin reactions

Recommendations for appropriate management of skin reactions, including guidance on dose-adjustments for clinically significant and/or intolerable skin reactions that are considered by the clinician to be causally related to osimertinib is provided in **Appendix D**, Guidance for the Management of Adverse Events in Studies using 80 mg osimertinib."

3.4.1.5 Diarrhea

Recommendations for appropriate management of diarrhea, including dose-adjustments for adverse events of diarrhea that are of CTCAE grade ≥3 or that are clinically significant and/or intolerable and considered by the clinician to be causally related to osimertinib, is provided in **Appendix D**, "Guidance for the Management of Adverse Events in Studies using 80 mg osimertinib."

3.5 ON STUDY ASSESSMENTS

Tumor samples will be obtained at baseline by a biopsy unless fresh tissue is available at screening. Patients will be seen on Days -1 and 7 (±2 days) of cycle 1, and on Day -1 of each subsequent treatment cycle. On study assessments can be performed within ±5 days of the specified time point, unless otherwise indicated. The following will be done:

- History and physical exam
- Laboratory evaluation: Hematologic and biochemical profile as listed in section **2.3**
- Cerebrospinal fluid analysis (cytology, cell counts, and protein and glucose levels) will be performed only in patients with suspected leptomeningeal disease.
- ECG
- Blood sample for correlative studies
- Saliva sample for detection of EGFR mutation
- Urine sample for correlative studies
- Tumor imaging will be performed every 56 days (every 2 cycles).
- At the time of progression if a patient is eligible for surgery as a form of LAT, then tissue sample will be obtained. For patients who are not eligible for LAT or a form of LAT that is not surgery (RT, RFA, cryoablation), then a mandatory biopsy will be performed, if clinically safe.

Note 1: If patients progress on osimertinib and are eligible for LAT, appropriate testing such as pulmonary function tests and a whole-body FDG-PET scan will be performed.

Note 2: If patients progress at the same site where LAT has been performed before, the progression will be considered to be a result of inadequate ablation and they will be considered for repeat LAT and again re-challenged with osimertinib if clinically feasible. Re-initiation of osimertinib treatment in this case also has to be within a month.

Note 3: Every attempt will be made to collect urine and saliva samples at each protocol specified timepoint. Collection of the urine and saliva samples is to be strongly pursued but is not required and may be waived at the discretion of the PI.

Before re-initiation of osimertinib following LAT, the following will be done.

- History and physical exam
- Laboratory evaluation
    - 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 (ALP), lactate dehydrogenase (LDH), bilirubin, albumin, creatinine kinase.
  - Baseline glomerular filtration rate (GFR) calculation.
  - Serum or urine beta-hCG for female patients of childbearing potential within 72 hours prior to therapy.
- ECG
- Tumor imaging
- Blood samples for correlative studies

After re-initiation of osimertinib, patients will be seen on day 7 (±2 days) and Day -1 of each subsequent treatment cycle (+/-5 days), then the following will be done.

- History and physical exam
- Laboratory evaluation: Hematologic and biochemical profile
- ECG
- Tumor imaging will be performed every 56 days (every 2 cycles)
- Blood sample for correlative studies
- Saliva sample for detection of EGFR mutation
- Urine sample for correlative studies
- At the time of second progression on osimertinib, a fresh tumor biopsy is optional.

An echocardiogram will be performed every 4 months (± 7 days) while the patient receives treatment.

After 30 days (±7 days) from treatment termination, the following will be obtained:

- History and physical exam
- Laboratory evaluation: Hematologic and biochemical profile
- ECG
- Research blood, urine and saliva collection

3.6 STUDY CALENDAR

Screening assessments must occur within 28 days prior to study drug initiation unless otherwise indicated.

Dosing cycles after cycle 1 may be delayed for up to two weeks to accommodate schedule conflicts, Federal holidays, inclement weather, etc.

Visit	**1** **Screening (within 28 days)**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**30 day post therapy visit[g]**	**Long term follow up**	**For details see Protocol Section**
Week		**1**	**2**	**5**	**9**	**13**	**17**	**21+** **(every 4 w unless otherwise specified)**			
Cycle		**1**		**2**	**3**	**4**	**5**	**6+**			
Written informed consent *(including tissue samples*)	X										
NIH Advance Directives Form [f]											
Demographics	X										
Confirmation of diagnosis and mutation status	X										
Height	X										
Physical examination and weight	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X										
Medical/surgical history	X	X	X	X	X	X	X	X	X		

Visit	**1** **Screening (within 28 days)**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**30 day post therapy visit[g]**	**Long term follow up**	**For details see Protocol Section**
Week		**1**	**2**	**5**	**9**	**13**	**17**	**21+** **(every 4 w unless otherwise specified)**			
Cycle		**1**		**2**	**3**	**4**	**5**	**6+**			
Inclusion/exclusion criteria	X										
12-lead ECG[a]	X	X	X	X	X	X	X	X	X		Section **6.4.3.1**
Vital signs	X	X	X	X	X	X	X	X	X		
Ophthalmologic evaluation	X										Section **6.4.4**
Echocardiogram	X						X (every 4 mths)				Section **3.5**
Treatment dispensed/returned		X	X	X	X	X	X	X			
Concomitant medication	X	X	X	X	X	X	X	X			
Adverse event review (AEs and SAEs)		X	X	X	X	X	X	X	X		
Blood samples for hematology and clinical chemistry	X	X	X	X	X	X	X	X	X		Section **2.3**
Beta-hCG	X[b]										
Research urine[h]		X	X	X	X	X	X	X	X		Section **3.5**

Visit	**1** **Screening (within 28 days)**	**2**	**3**	**4**	**5**	**6**	**7**	**8+**	**30 day post therapy visit[g]**	**Long term follow up**	**For details see Protocol Section**
Week		**1**	**2**	**5**	**9**	**13**	**17**	**21+** **(every 4 w unless otherwise specified)**			
Cycle		**1**		**2**	**3**	**4**	**5**	**6+**			
Research blood		X	X	X	X	X	X	X	X		Section **3.5**
Research saliva[i]		X	X	X	X	X	X	X	X		Section **3.5**
MRI or CT of the brain	X										Section **2.3**
CSF analysis[e]	X										
Computed tomography (CT) scan of the chest/abdomen/pelvis	X	Radiologic measurements should be performed every 8 weeks.									Section **3.5**
Tumor measurement	X	Tumor measurements are repeated every 8 weeks									Section **3.5**
Tumor biopsy[c]	A mandatory tumor biopsy will be obtained at baseline (unless fresh tissue available from screening) and at first progression. At second progression, a fresh tumor biopsy is optional.										Section **3.5**
Annual visit or phone call to assess survival, progression and new cancer therapy										X	Section **3.5**

a: 12-lead ECGs can be performed on day -1 (+/- 5 days) of each cycle.

b: Serum pregnancy test (women of childbearing potential) within 72 hours prior to therapy.

c: Tumor samples will be obtained at baseline (unless fresh tissue available from screening) by a mandatory biopsy. At the time of first progression on osimertinib if a patient is eligible for surgery as a form of LAT, then tissue sample will be obtained for all correlative

studies. For patients who are not eligible for LAT or a form of LAT that is not surgery (radiation, radiofrequency ablation, cryoablation), then a mandatory biopsy will be performed, if clinically safe, to obtain tissue for correlative studies. If a biopsy at this time is not clinically safe, then tissue obtained from the previous biopsy for the mutation testing needed for eligibility for this protocol may be used. At the time of second progression on osimertinib, a fresh tumor biopsy is optional.

e: Cerebrospinal fluid analysis (cytology, cell counts, and protein and glucose levels) will be performed only in patients with suspected leptomeningeal disease

f: As indicated in section **12.3**, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended but is not required.

g. The post treatment visit should occur 30 days (± 7 days) after terminating treatment. This applies to both the first treatment course and second, if applicable. The assessments listed refer to those that will be performed if the patient is seen in clinic **(first course and second course)**. If the patient is unable to return to the clinic for the follow up visit, adverse event assessments will be performed by telephone or email. We will request that required labs and ECG be performed locally and provided to us, and if the patient has visited a local oncologist in this timeframe, the progress notes will also be requested. If any aspect of the required assessments as listed in the calendar is not performed, it will be recorded and reported to the IRB as a deviation.

h. Every attempt will be made to collect urine samples at each protocol specified timepoint. Collection of these samples is to be strongly pursued but is not required and may be waived at the discretion of the PI.

i. Every attempt will be made to collect research saliva samples at each protocol specified timepoint. Collection of these samples is to be strongly pursued but is not required and may be waived at the discretion of the PI.

3.7 RADIATION THERAPY GUIDELINES

Patients with oligoprogressive disease will be referred for radiation therapy if they are not eligible for surgery as a form of LAT. The treating radiation oncologist will evaluate the feasibility of safely treating the site(s) of progressive disease, for which he/she may require a CT simulation/planning session. He/she may determine at any time during the consult/simulation/planning process that radiation therapy is not feasible.

Each site of progressive disease should be treated to a definitive dose. Brain metastases may be treated with whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or the combination of WBRT + SRS. Sites of extracranial disease may be treated with conventionally fractionated external beam radiation therapy (EBRT) or stereotactic body radiation therapy (SBRT)/stereotactic ablative radiotherapy (SABR). The specific dose and fractionation scheme is at the discretion of the treating radiation oncologist. If multiple sites are to be treated with radiation therapy, they may be treated either concurrently or sequentially at the discretion of the treating radiation oncologist.

As of Amendment J, patients may receive radiation therapy concurrently with osimertinib. The type and amount of radiation therapy to be administered will be determined by the treating radiation oncologist.

In the opinion of the treating radiation oncologist, if any site cannot be safely treated to a definitive dose for any reason, patient will be considered not to be eligible for radiation as a form of LAT. Palliative radiation may still be given if clinically indicated. Patients will not be eligible for LAT in such cases.

Each patient must be specifically consented for unknown side effects and/or toxicities, either acute or chronic, resulting from the prior and subsequent osimertinib treatment in addition to radiation treatment under this protocol.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.8.1 Criteria for removal from protocol therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression, per RECIST*,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) as described in section **3.4**,
- Delay of treatment of ≥ 4 weeks,
- Patient decides to withdraw from the study therapy
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Severe non-compliance with the study protocol

Note: *Some subjects may be eligible for re-treatment if removed for this reason. See Section

3.2.

Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study, without prejudice to further treatment. A subject that decides to discontinue investigational will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up for minimum of 4 weeks after the final dose of osimertinib. All study drugs should be returned by the subject.

3.9 FOLLOW UP

Patients will be followed either with clinic visits or phone interviews yearly until death. Patients removed from treatment for unacceptable adverse event(s) will be followed clinically until resolution or stabilization of the adverse event, and then via clinic visits or phone interviews yearly until death.

The following information will be collected:

- Date of follow up
- Is patient dead or alive?
- If dead, document exact date of death.
- Further treatment(s), if any
- Document date of disease progression

3.10 OFF STUDY CRITERIA

At any time, patients are free to discontinue treatment and withdraw from the study (i.e., study treatment and assessments). A patient who decides to discontinue treatment and assessments will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up; all investigational product should be returned by the patient or caretaker. The term withdrawal from the study refers to both the discontinuation from the treatment and study assessments. Withdrawn subjects will not be replaced.

Once a patient has been removed from study, no further data can be collected; therefore, with completion of the duration of follow-up described in Section **3.9**, the criteria for removal from study are:

- Lost to follow-up
- Death
- The patient decides to withdraw from the study.
- Investigator discretion

The reason for study removal and the date the patient was removed must be documented in the database.

3.11 OFF-PROTOCOL THERAPY AND OFF-STUDY PROCEDURE

Authorized staff must notify the NCI Central Registration Office (CRO) when a patient is taken off protocol therapy and when a subject is taken off study. A Participant Status Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 CONCOMITANT MEDICATIONS

Once enrolled all patients must try to avoid concomitant use of medications, herbal supplements and/or ingestion of foods with known potent inhibitors or inducers of CYP3A4 whenever feasible; however, patients may receive any medication that is clinically indicated for treatment of adverse events. Such drugs must have been discontinued for an appropriate period before they enter screening and for a period of 3 months after the last dose of osimertinib. All concomitant medications should be captured on the CRF. Guidance on medicines to avoid, medications that require close monitoring and on washout periods is provided (see **Appendix B**).

If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 (see above), should be maintained on it throughout the study period. Patients taking concomitant medications whose disposition are dependent upon CYP3A4, and BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Additionally, due to the potential CYP450 and p-glycoprotein induction risk exposure of drug that are metabolized by CYP3A4, CYP1A2 or CYP2C or whose deposition is mediated by p-glycoprotein could also be reduced and should also be monitored for reduction in therapeutic activity (especially those which have narrow therapeutic index). Guidance on medications to avoid, medications that require close monitoring and on washout periods should be provided.

Patients should be advised of the potential reduction in effectiveness of oral hormonal contraceptives (due to CYP3A4 induction) when used with osimertinib. A change to a non-oral method of contraception (e.g. IUS Levonorgestrel Intra Uterine System, Medroxyprogesterone injections), or addition of a barrier method (e.g. condoms, diaphragm) to the primary hormonal method, is recommended prior to the commencement of treatment.

Up to 1.5-fold increase in exposure may occur in statin exposure when co administered with osimertinib. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin label. Monitoring of low- density lipoprotein (LDL) cholesterol levels is advised. If the patient experiences any potentially relevant adverse events suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, the statin should be stopped, creatine kinase (CK) levels should be checked, and any appropriate further management should be taken.

Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

4.1.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

4.1.2 Supportive care guidelines

- **Nausea/vomiting** may be treated with anti-emetics.
- **Diarrhea** should be managed with loperamide: 4 mg at first onset, then 2 mg every 2-4 hours until diarrhea is controlled (maximum = 16 mg loperamide per day).
- **Hand-foot syndrome** may be treated with topical emollients (such as Aquaphor), topical/systemic steroids, and/or antihistamine agents. Vitamin B6 (pyridoxine; 50-150 mg orally each day) may also be used. Avoid exposure to heat, hot water, pressure, or friction. Use of soft, well-fitting shoes may help, as may use of acetaminophen if needed for analgesia.
- Patients with **neutropenic fever** or infection should be evaluated promptly and treated with IV antibiotic therapy or therapeutic colony-stimulating factors as appropriate following the ASCO guidelines.[68] Packed red blood cell and platelet transfusion should be administered as clinically indicated. Erythropoietic agents may be used at the discretion of the treating physician.

4.1.3 Additional Restrictions

If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 (see above), should be maintained on it throughout the access program period (30 days post-last dose). Patients taking concomitant medications whose disposition is dependent upon CYP3A4 and breast cancer resistance protein (BCRP) and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Patients taking concomitant medications whose disposition is dependent upon CYP3A4, CYP1A2, CYP2C or p-glycoprotein and which have a narrow therapeutic index should be closely monitored for reduction in therapeutic activity as a result of the reduced exposure of the concomitant medication while receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see **Appendix B**).

Up to 1.5-fold increase in exposure may occur in statin exposure when co-administered with osimertinib. It is recommended that the starting and maintenance dose of statins should be as low as possible and should be guided by the statin prescribing information.

Patients taking warfarin should be monitored regularly for changes in prothrombin time or international normalized ratio (INR).

Patients who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving treatment with osimertinib until at least one week after symptoms have resolved. If a patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events, they must discontinue wearing their contact lenses until at least one week after treatment with osimertinib is permanently discontinued. Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed to by an access program doctor, at any time during the access program until 1

week after osimertinib has been permanently discontinued. Patients should consult their clinician promptly if they have any concerns.

5 BIOSPECIMEN COLLECTION

Research tissue samples will initially be sent to the laboratory of Dr. Doug Figg (see Section **5.1.1**), and samples for clinical testing will be directly transported to the Laboratory of Pathology. All blood, urine, and saliva samples will initially be sent to the laboratory of Dr. Doug Figg (see Section **5.1.2**), where they will be stored until ready for transfer to the recipient labs for the correlative studies as described below. Coded, linked data will be shared with collaborators as specified below, however, the collaborators will not have access to the key that links the data back to the patients in which it was obtained.

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1.1 Pathology correlative studies

5.1.1.1 Timing

Tumor samples will be obtained at the following times.

- At baseline prior to initiation of the study treatment
- At the time of first progression on osimertinib
- At the time of second progression on osimertinib, a fresh tumor biopsy is optional.

5.1.1.2 Tissue sampling and handling

An excision biopsy of accessible lymph node or cutaneous nodule, or CT or bronchoscopy guided core needle biopsy using a 16-18 gauge needle will be obtained at baseline. At the time of first progression on osimertinib, if a patient is eligible for surgery as a form of LAT, then tumor sample will be obtained for all correlative studies. For patients who are not eligible for LAT or a form of LAT that is not surgery (radiation, radiofrequency ablation), then a mandatory biopsy will be performed, if clinically safe, to obtain tissue for correlative studies. If a biopsy at this time is not clinically safe, then tissue obtained from the previous biopsy for the mutation testing needed for eligibility for this protocol may be used.

Material released for research studies will be documented on form NIH 2803-1 Request & Certification for Research Procurement of Human Biological Materials. Initial processing of samples for research will depend on the size of the tumor biopsy. For core biopsies the research sample will typically consist of up to 4 cores. The first core will be processed and stored in the NCI Laboratory of Pathology.

The second core (when successfully obtained without additional risk to the patient) will be snap frozen in a microcentrifuge vial in liquid nitrogen. The third core will be frozen in an OCT block in Liquid Nitrogen. The investigators may decide to use either the 3rd or 4th core to generate a cell line or patient-derived xenograft (PDX). These research samples will be stored in Dr. Figg's laboratory (10/3B52) at -80°C on site.

Tumor may be viably frozen, typically at concentrations of 20-100x10^{6}/mL in FBS with 10% DMSO using a temperature controlled freezing process to optimize sample viability. Samples will be transferred to liquid Nitrogen tanks for long-term storage.

Attempts will be made to generate cell lines from viable tumor or normal lung tissue and body fluids, such as pleural effusion in a subset of patients.

Tumor tissue from a subset of patients may also be incorporated as xenograft in NOD/SCID mice to grow tumor tissue in vivo as patient derived xenografts (PDX).

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.

5.1.1.3 Studies

5.1.1.3.1 Mutational analysis will be conducted using the cancer gene mutation panel and whole exome and transcriptome sequencing. Whole genome sequencing will be performed in select cases. The cancer gene mutation panel will be performed in the Ion Torrent platform in Dr. Mark Raffeld's Molecular Pathology Core. These genes include *ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53,* and *VHL*.

5.1.1.3.2 Proteomic approaches using mass spectrometry, luminex assay, Simple Western assay (NanoPro) and reverse phase protein array (RPPA) will be used for quantitation of proteome and post-translational modifications, including phosphorylation to identify changes in signaling pathways before and after treatment with osimertinib.

5.1.1.3.3 Pre- and post- treatment tumor tissue will also be grown in patient-derived xenograft (PDX) models to study mechanisms of resistance. Efforts will be made to generate cell lines from these tissues. Preclinical evaluation in murine cancer models that emulate the complexities of human cancers and yet remain tractable for therapeutic and diagnostic discovery has recently shown success in guiding clinical research and is expected to improve success rates, reduce cost, accelerate timelines, and minimize the human toll exacted by current practices wherein efficacy is determined first in patients. In early passages, PDX tumors typically retain the histologic and molecular heterogeneity and stromal composition characteristic of those in patients and thus are essentially patient "avatars". As such, human target specificity is retained allowing for direct evaluation of lead human-specific therapeutics that are in clinical development. Although host mouse stroma incorporates into tumors with passage, even serially established models have been valuable for first-line evaluation of many therapeutics. Additionally, PDX models have been demonstrated as powerful tools for the identification of drug resistance mechanisms[69] and targets for second-line treatment[70]. Programs are also underway to employ PDX models to help guide individual patient therapy decisions[71, 72]. Therefore, use of PDX models is relevant to the study of resistance to osimertinib and potential approaches to abrogate resistance. PDX models will be established from fresh tumor material in collaboration with the Center for Advanced Preclinical Research (CAPR), at NCI-

Frederick. CAPR, founded by the Center for Cancer Research (CCR) under the direction of Dr. Terry Van Dyke, is a dedicated organization adept in the use of modern mouse cancer models for applied preclinical research. Its mission is to develop, disseminate, and apply reproducible preclinical practices effective in guiding clinical research toward improved cancer patient management. CAPR has extensive expertise in preclinical research utilizing modern murine cancer models of a variety of cancer types. Broadly applicable and specialized methodologies have been optimized and are executed under standard operating procedures. Coded, linked samples will be sent to:

Zoe Weaver Ohler, PhD
Principal Scientist/Team Leader, Preclinical Evaluation
Center for Advanced Preclinical Research
Leidos Biomedical Research, Inc.
Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St. Bldg. 539
Frederick, MD 21702

5.1.1.3.4 A correlative study of treatment response to novel targeted agents or combination targeted agents along with osimertinib will be conducted using CANScript™ – a platform to grow patient derived tumor tissue in three dimensional cultures along with proprietary tumor microenvironment components. This study will be done in collaboration with Mitra Biotech in a subset of patients. Osimertinib -resistant tumor tissue obtained at surgery for LAT will be cultured as explants using CANScript™. Novel combination agents or specific targeted agents will be used to test sensitivity of these osimertinib -resistant tumors to other targeted agents. Positive "hits" will be then used in the PDX models generated from the same patient to assess tumor response in vivo. If this approach to identify and validate novel targeted agents is successful, the protocol will be amended to potentially use this information to treat patients after PFS2. For each sample collection a "kit" will be provided by Mitra Biotech that will contain sterile labeled containers with sterile isotonic proprietary buffer containing antibiotics. The collected core/s of tumor tissue will be coded and linked and transferred into the provided containers and shipped in temperature controlled containers provided by the company. In addition, 10 ml of blood will be collected in BD Vacutainer SST™ tubes (serum separating tubes) and a CPT (cell preparation tube): BD Vacutainer CPT™ with sodium citrate. These coded, linked samples will be sent to Mitra Biotech at the following address:

Parker Cassidy
Laboratory Director
Mitra Biotech
12 Gill Street
Suite 3150
Woburn, MA 01801
339 999-2300
info@mitrabiotech.com

5.1.1.3.5 Proteo-genomics data analysis will be done in collaboration with Dr. Olga Vitek at Northeastern University. Coded, linked genomics or proteomics data generated at the NCI will be sent to Dr. Vitek for bioinformatics analysis. Dr. Vitek's group will perform bioinformatics and statistical analysis on the data. Data will be transferred securely, and no patient identification will be transferred.

The data will be sent to:

Olga Vitek, Ph.D.
Northeastern University
440 Huntington Avenue, 310F West Village H
Boston, MA 02115
o.vitek@northeastern.edu
617 373-6305
https://www.ccis.northeastern.edu/people/olga-vitek/

5.1.1.3.6 Analysis of genomic data will be completed in collaboration with Dr. Anna Panchenko at the National Library of Medicine. Coded, linked genomic data generated at the NCI will be sent to Dr. Panchenko for bioinformatic analysis using a secure drive. Using this data, Dr. Panchenko's group will evaluate the evolution of tumor mutations. Coded, linked data will be sent securely, and no patient identification will be transferred.

The data will be sent to:

Anna Panchenko, M.D.
NIH/National Library of Medicine
Computational Biology Branch
8600 Rockville Pike
Building 38A Room 6N607
Bethesda, MD 20894
301-435-5891
panch@ncbi.nlm.nih.gov

5.1.1.3.7 Proteogenomics analysis (Collaboration with S. Cenk Sahinalp, PhD)

Dr. Sahinalp's group will perform a temporal proteogenomic analysis of genomics and proteomics data obtained from the existing studies performed in this study. WES, RNA-seq and mass spectrometry-based proteomics data obtained from the experiments performed on the tumor tissue obtained from the mandatory biopsies will be used by Dr. Sahinalp's group to perform further bioinformatics analysis for molecular characterization of tumor evolution. In particular, fusion and structural variation discovery tools developed by Dr. Sahinalp's group such as defuse, nFuse, MistrVar, and destruct for exomic and transcriptomic sequence analysis will be used to match breakpoint signals with novel peptide signals from mass spectrometry data through their ProTie pipeline. Tumor phylogenies will be obtained and conserved evolutionary trajectories involving DNA, RNA and protein data will be characterized. Coded, linked NGS and mass spectrometry-based proteomics data

without patient identifiers will be sent to:

Dr. S. Cenk Sahinalp, PhD
Cancer Data Science Laboratory
National Cancer Institute
Building 10, Room 6N119
Bethesda, MD. 20892
Ph: 240-858-7117

5.1.1.3.8 Collaboration with Dr. Ramaswamy Govindan at Washington University

Genomics analysis on select tumor samples from this study will be performed at the McDonnell Genome Institute of the Washington University School of Medicine in collaboration with Dr. Govindan. Coded tumor samples without patient identifiers will be sent to Dr. Govindan's laboratory. WES, WGS (in a subset of samples sent) and RNA-seq will be performed on select tumor samples using the genomics core at Washington University. Coded linked sequencing data on samples analyzed at the NCI will also be sent to Dr. Govindan's group for further bioinformatics analysis and comparing with the data obtained at Washington University. The tumor tissue and the sequencing data will be sent to:

Dr. Ramaswamy Govindan
Anheuser Busch Chair in Medical Oncology
Director, Section of Medical Oncology
Washington University School of Medicine
660 S Euclid Avenue
Campus Box 8056
St. Louis, MO 63110
Phone: 314-747-7405/314-362-5737

5.1.1.3.9 PDX Models - CAPR

Tumor tissue of selected patients will be grown in patient-derived xenograft (PDX) models to study mechanisms of resistance. Efforts will be made to generate cell lines from these tissues. Preclinical evaluation in murine cancer models that emulate the complexities of human cancers and yet remain tractable for therapeutic and diagnostic discovery has recently shown success in guiding clinical research and is expected to improve success rates, reduce cost, accelerate timelines, and minimize the human toll exacted by current practices wherein efficacy is determined first in patients. In early passages, PDX tumors typically retain the histologic and molecular heterogeneity and stromal composition characteristic of those in patients and thus are essentially patient "avatars". As such, human target specificity is retained allowing for direct evaluation of lead human-specific therapeutics that are in clinical development. Although host mouse stroma incorporates into tumors with passage, even serially established models have been valuable for first-line evaluation of many therapeutics. Additionally, PDX models have been demonstrated as powerful tools for the identification of drug resistance mechanisms and targets for second-line treatment. Programs are also underway to employ PDX models to help guide individual patient therapy

decisions. PDX models will be established from fresh tumor material in collaboration with the Center for Advanced Preclinical Research (CAPR), at NCI-Frederick. CAPR, founded by the Center for Cancer Research (CCR), is a dedicated organization adept in the use of modern mouse cancer models for applied preclinical research. Its mission is to develop, disseminate, and apply reproducible preclinical practices effective in guiding clinical research toward improved cancer patient management. CAPR has extensive expertise in preclinical research utilizing modern murine cancer models of a variety of cancer types. Broadly applicable and specialized methodologies have been optimized and are executed under standard operating procedures.

5.1.1.3.10 Tumor Microenvironment - Medgenome

Medgenome offers cancer immunotherapy solutions which help in identifying biomarkers for patient selection, monitoring durability of response, evaluating mechanisms of drug unresponsiveness/resistance, mapping gene expression to pathways and identifying cancer vaccine candidates. We will use NGS data (RNA-seq and WES) from patients under this protocol for tumor microenvironment analysis solution that can be used as a stand-alone solution to analyze the tumor microenvironment at the cellular and molecular level, or can complement IHC and FACS-based approaches. We will also use Medgenome's NGS based neo-antigen prediction and neo-epitope prioritization solution that involves HLA binding peptides identification, TCR binding peptides identification, Structural Analysis of peptides to prioritize TCR binding, Peptide Processing and TAP binding. MedGenome has a CLIA certified, CAP accredited and ISO 15189 compliant NGS lab in Foster City, California. Coded, linked data will be sent to Medgenome. The contact information is:

Dr. Amit Chaudhuri, VP, R&D
Medgenome
348 Hatch Drive
Foster City, CA 94404
888 440-0954
amitc@medgenome.com

5.1.1.4 Plasma samples for next generation targeted sequencing – Inivata, Inc.

Coded, linked patient plasma samples for next generation targeted sequencing will be sent to Inivata, Inc., a global clinical cancer genomics company utilizing a proprietary liquid biopsy platform, Invision™, to transform patient care. Inivata will provide next-generation sequencing testing on circulating tumor DNA isolated from plasma utilizing the Invision™ platform. This amplicon-based platform interrogates 36 genes for common somatic changes found in human cancer and was developed with a focus on therapeutically actionable somatic changes.

Utilizing a target of 2 mls of plasma, DNA will be isolated, quantified and profiled by the InVision platform. Samples with codes (the key for patient identification retained only at NCI) will be provided to Inivata and will be sent to Inivata's CLIA accredited testing laboratory located in Research Triangle Park, NC. Data will be aggregated and communicated after each batch of samples sent for testing. Inivata will be available to provide their expertise in assisting with the interpretation of the sequencing results as needed. Coded, linked patient plasma

samples will be sent to:

Greg Jones
Inivata, Inc
7020 Kit Creek Road
Suite 140
Research Triangle Park, NC 27709
+1-919-313-9687

5.1.1.5 Blood and Tissue Samples – FDA

Plasma and tissue samples from select patients will be sent to the FDA for NGS studies in collaboration with Dr. Julia Beaver's group at the FDA, who will run a targeted NGS panel, exome sequencing (WES) and/or TCR (T-cell receptor) sequencing on the samples. The platform is Illumina NextSeq500. At this time they plan to use the UMI Toolkit and TruSeq 170 library prep kits from Illumina to prepare the ptDNA for sequencing.

5.1.1.6 Blood samples for Cell Free DNA Isolation

Patients may undergo an optional blood collection of two (2) additional 10 ml Cell-free DNA BCT tubes from Streck which will be used for cell-free DNA (cfDNA) isolation. These tubes are blood collection tubes which stabilize nucleated blood cells. The proprietary preservative prevents the release of genomic DNA, allowing isolation of high quality cell free DNA. These tubes will preserve cfDNA in a blood sample for up to 14 days in room temperature. Our existing methodology of plasma isolation from EDTA containing purple top tubes with twice centrifugation will be compared with that from Cell-free DNA BCT Streck tubes following manufacturer's instructions. The amount of cfDNA, the quality and downstream analysis of mutation detection by ddPCR will be compared. A cost-benefit analysis will be performed after at least 10 patients' blood have been collected and analyzed by the two methodologies and a decision will be made as to use the Streck tubes or continue with our standard EDTA containing purple top tubes.[73]

Method for plasma isolation: Blood tubes will be centrifuged at 1600Xg for 10 minutes at RT using a swing-out rotor and a smooth braking profile. Using a 1ml pipet, plasma will be transferred to a fresh 15 ml collection tube leaving around 500µl plasma in the blood collection tube to avoid transfer of cellular fraction. The supernatant will be centrifuged a second time at 6,000 X g for 10 min to remove any residual blood cells. The resulting supernatant will again be transferred to a fresh collection tube leaving around 300µl at the bottom to prevent transfer of any cellular debris. Plasma will be gently mixed by pipetting and aliquoted in cryogenic vials and frozen at -80C until DNA extraction.[73]

5.1.1.7 Collaboration with Dr. Haixu Tang, Indiana University

This collaboration is aimed at building a pipeline for neoantigen discovery for the purpose of cancer vaccine development and T cell receptor (TCR)-directed cellular therapy. Two datatypes will sent to Dr. Tang's group. One is mass spectrometry-based immunopeptidomics data from Figg laboratory in Cancer Signaling Networks section of TGMB. The other is whole exome sequencing (WES) and RNA-seq data from the analysis of tumor tissue from patients in our clinical study. ImmuNOVO software suite built in Dr. Tang's group will be used process the

immunopeptideomics data to provide better identification of neoantigens. RNA-seq and WES data will be used for mutation detection and quantification. The NGS data will also be utilized for HLA typing, confirming the typing output from ImmuNOVO. Artificial intelligence (AI)-models will be built based on neoantigens predicted from immunopeptideomics along with the RNA-seq and WES data, including the mutation detection, quantification and HLA typing.

All sequencing data will be coded and linked. The code is retained by investigators of this clinical protocol.

The immunopeptidomics, WES and RNA-seq data will be sent to:

Dr. Haixu Tang
Professor, Department of Computer Science
School of Informatics, Computing, and Engineering
Indiana University, Bloomington
700 N. Woodlawn Avenue
Bloomington IN 47408
Email: hatang@indiana.edu

5.1.1.8 Collaboration with Gritstone Oncology

WES and RNA-seq data from sequencing studies performed on tumor tissue from patients will be sent to Gritstone Oncology. All sequencing data will be coded without any patient information attached. The code is retained by investigators of this clinical protocol. Gritstone will first analyze this data by applying the Gritstone neoantigen prediction algorithm, EDGE.

For each patient with a putative EGFR neoantigen (to be identified by applying the Gritstone neoantigen prediction model EDGE to the mutation calls and HLA types from the individual patient tumor exome data), one or both of the following will be sent:

(1) Fresh frozen resected tumor, 10-50 mg, snap frozen in liquid nitrogen, stored at <-80C

(2) PBMCs cryopreserved within 4-5h of collection, viable and functional upon thaw (>10^7 PBMCs total)

Gritstone will perform on these samples the following:

- Resected tumors: transcriptome sequencing, if not done already and targeted mass spectrometry in triple quadrupole (QQQ) mass spectrometer will be performed for EGFR mutations and any other shared neoantigen
    - HLA types would be confirmed from txTomes; txTomes also used to assess level of EGFR expression and other genes
- PBMCs: Standard immune assays (such as elispot or tetramer) to identify T cell responses against EGFR or any another shared neoantigens
- Optionally, depending on interest and in part on amount of sample available: HLA presentation or T cell recognition of other tumor specific antigens such as cancer testis antigens.

The sequencing data will be sent to Dr. James Sun:

Dr. James Sun
40 Erie Street, Suite 120,
Cambridge MA 02139
Ph : 857.327.9805
jsun@gritstone.com

Tumor tissue for MS/MS analysis will be sent to Dr. Jennifer Busby:

Jennifer Busby, PhD
Senior Director of Mass Spectrometry and Proteomics
Gritstone Oncology, Inc.
40 Erie Street; Suite 120
Cambridge, MA 02139
Office: 857-327-9806
Cell: 561-889-3492
jbusby@gritstone.com
www.gritstone.com

5.1.1.8.1 Plasma Samples

After the blood samples are spun down within two hours of collection, the plasma portion will be stored in a -80°C freezer until shipment via FedEx to:

ATTN: Elliot Rosen
DBRR III/OBP/OPQ/CDER
Food and Drug Administration
10903 New Hampshire Ave,
Bldg 52/72, Room 2248,
Silver Spring, MD 20993
Phone: 240-402-7353
Email: Elliot.Rosen@fda.hhs.gov

During shipment, samples will be stored on dry ice and sealed in a Styrofoam container in the absence of any PHI. Upon arrival, samples will be immediately stored in a locked -80°C freezer (number 859) in building 75 room G631 at The Food and Drug Administration until use.

These plasma samples will undergo DNA extraction and library preparation followed by targeted or whole exome next generation sequencing (NGS) on the CDER/FDA Illumina NextSeq500. Genomic data will be analyzed and the ptDNA portion elucidated from the underlying normal DNA using various algorithms. Subsequent analysis of mutational load, and somatic alterations in the ptDNA will be performed and quantified. Additional analyses including evaluation of alternative transcripts, base substitutions, mutations, gene fusions, allele-specific expression patterns will also occur. Subsequent samples will also be sequenced and analyzed. Further expression analysis may also occur.

5.1.1.8.2 Tumor samples

If available, matched specimens from primary tumors collected will be sent to FDA as well to the same address as above, either FFPE or fresh frozen samples, in order to screen for somatic mutations and genomic rearrangements using NGS from samples obtained at the time of surgery or in the advanced/metastatic setting. As available, concordance of somatic mutations in tissue and plasma will be compared and followed longitudinally, correlated to clinical course.

5.1.1.8.3 Additional Information

Any data or results generated from this project are intended for research purposes only and will not presently change the diagnosis or management of individual patients from whom the data were collected; therefore, no information will be provided back for inclusion in the medical records of the participants whose data are used.

5.1.2 Blood and urine correlative studies

All blood and urine samples will initially be sent to the laboratory of Dr. Doug Figg (BPC), where they will be stored until ready for transfer to the recipient labs for the correlative studies as described below.

Please e-mail the BPC lab at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact the BPC lab at NCIBloodcore@mail.nih.gov .

5.1.2.1 Timing

Blood and urine samples will be obtained at the following times. Note: Urine samples for correlative studies will be collected when feasible. Collection of these urine samples is not required and may be waived at the discretion of the PI

- For cycle 1, blood and urine samples will be obtained on Days -1 (±2 days) and 7 (±2 days) of cycle 1.
- For subsequent cycles, blood and urine samples will be obtained Day -1 (±5 days) of each subsequent treatment cycle.
- Blood and urine samples will be collected at the 30 day post therapy visit.

5.1.2.2 Tissue sampling and handling

Phlebotomy will be performed by standard procedures. Sampling limits established by the NIH Clinical Center will be adhered to: no more than 550 ml per 8 week interval will be drawn. There is minimal discomfort associated with the procedure and a very small chance of bruising, bleeding, or infection. About 45 ml of random urine specimen will be collected. The specimen should be collected in a sterile cup and placed on ice. A 24 hour urine specimen may also be collected. Each patient sample set will be assigned a unique patient identifier.

One 10 ml red top tube will be used to isolate serum samples. Serum will be snap frozen and stored in liquid nitrogen for future proteomic biomarker studies.

Red top tubes

i) Allow the blood to clot by standing at room temperature for 30 minutes.
ii) Separate serum from cells by centrifuging at 4 degrees C for 5 minutes at 1200g.
iii) Pipette aliquots of 1.5mLs each into two 2mL cryovials.
iv) Freeze immediately at -20C or lower
v) Maintain in -80C freezer or liquid nitrogen for storage

Two 10cc lavender top tubes will be used for plasma isolation for circulating tumor DNA (ctDNA) extraction and proteomics studies and one additional 10 cc lavender top tube will be collected for isolation of PBMC, circulating tumor cells (CTCs), other viable cell types, including immune subsets, and exosomes and delivered to Jane Trepel's laboratory (Phone: 240-760-6330; e-mail trepel@helix.nih.gov). Isolated PBMC and circulating tumor cells will be analyzed by FACS, stored in liquid nitrogen, or grown in culture if feasible.

5.1.2.3 Studies

- Serum and plasma DNA will be isolated and analyzed for genomic alterations by next generation sequencing or digital droplet PCR (ddPCR).
- Serum and plasma samples will also be analyzed for proteomic and metabolic profiling to correlate potential biomarkers with treatment response and resistance.
- Urine samples will be used for metabolomic studies and proteomic studies, including urinary exosome analyses in the Laboratory of Metabolism under the direction of Dr. Frank Gonzalez and the Laboratory of Human Carcinogenesis under the direction of Dr. Curtis Harris.

5.1.2.3.1 Targeted sequencing of ctDNA

Blood samples will be collected to evaluate cancer gene mutations and genome markers during therapy. Analysis of liquid biopsies can potentially improve disease subclassification, improve monitoring of disease burden and response to treatment, and provide new knowledge of resistance mechanisms during disease relapse in patients with NSCLC. Targeted Next-Generation Sequencing (NGS) will be performed with a panel of approximately 300 cancer related genes or their subset, and other genomic aberrations. Analysis will be performed to determine the association with clinical response. Blood samples will be obtained at baseline prior to therapy after therapy has been completed. For existing samples, 2 cc of EDTA plasma will be obtained per sample timepoint. For prospective sample collection, EDTA plasma will be isolated from 10 ml of blood at Dr. Figg's lab within 5 hours of blood draw. The plasma samples (4-5cc) will be stored in two 3cc tubes at -80°C. The coded, linked samples will be sent for analysis to:

Liang Cao, Ph.D.
Head, Molecular Targets Core Genetics Branch
NCI – Center for Cancer Research
37 Convent Dr. MSC 4265

Bldg 37, Rm 6134
Bethesda, MD 20892-1906
Phone: (240) 760-6893
Cell: (240) 271-3786
caoli@mail.nih.gov

5.1.3 Saliva correlative studies

5.1.3.1 Timing

Every attempt will be made to collect saliva samples at the following times:

- For cycle 1, saliva samples will be obtained on days 1 and 7.
- For subsequent cycles, saliva samples will be obtained every four weeks (± 5 days).
- Saliva will be collected at the 30 day post therapy visit

5.1.3.2 Tissue sampling and handling

Saliva samples will initially be sent to the laboratory of Dr. Doug Figg (CPP), where they will be stored until ready for transfer to the recipient lab for the correlative studies as described below.

The saliva will be collected using the PureSal™ oral specimen collection system from Oasis Diagnostics. This device is a non-invasive rapid collection system for isolating DNA/cell free RNA or proteins in a single step. The saliva procured by this system is immediately stabilized and available for downstream applications, such as PCR, genotyping, sequencing, and proteomics. The coded, linked saliva samples collected using this kit will be sent at room temperature to:

David T.W. Wong DMD, DMSc
University of California Los Angeles
Felix & Mildred Yip Endowed Professor & Associate Dean of Research
School of Dentistry
Director, Center for Oral/Head & Neck Oncology Research
10833 Le Conte Avenue, 73-017 CHS
Los Angeles CA 90095
310 206-3048
dwong@dentistry.ucla.edu

5.1.3.3 Studies

Dr. David Wong's group at UCLA has developed a method of detecting EGFR mutations in body fluids using a technology that is based on electric field-induced release and measurement (EFIRM). This uses a multiplexible electrochemical sensor that can detect EGFR mutations in bodily fluids[74, 75]. EFIRM-liquid biopsy (eLB) showed near 100% concordance with biopsy-based genotyping for actionable mutations in non-small cell lung carcinoma (NSCLC) lung cancer patients in two independent blinded clinical studies in Taiwan[75] and China (preliminary data). In collaboration with Dr. David Wong and his group at UCLA, we will detect EGFR mutations from serial saliva collection from patients and correlate the findings with the mutation

testing from plasma DNA and tumor tissue specimens. The eLB will be performed on an ACEA 96-well electrochemical plate (E Plate 96), manufactured by ACEA Biosciences Inc. (San Diego CA) under GMP. To avoid imprecision due to human operation, all the liquid handling procedures will be done with the BioMek 3000 robotic system and BioRad platewasher. The detection device is a 96-channel electrochemical workstation. Electrochemical signals for all channels on the electrochemical plate are analyzed simultaneously, in real-time.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through the Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.2.1 Figg Laboratory

All research specimens will be coded.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or unanticipated destruction of samples per section **7.2.1** .

A full chain of custody is maintained for all samples throughout their lifecycle. The Principal Investigator keeps full traceability of collected biological samples from the subjects while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival. The PI keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers. Samples retained for further use should be documented and stored during the entire life cycle.

Freezer problems, lost samples or other problems associated with samples that meet expedited reporting requirements (see section **7.2.1**) will also be reported.

5.2.2 Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not placed in paraffin blocks is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases,

this approval has been obtained via the original protocol on which the patient was enrolled.

5.2.3 Laboratory of Jane Trepel

Samples will be processed immediately by the Trepel laboratory. Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. Specimen labels will indicate: protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total volume collected, as appropriate. The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

5.3 CLINICAL PHARMACOLOGY PROGRAM

5.3.1 Procedures for sample data collection for the Clinical Pharmacology Program:

- All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP. This is a secure program, with access to PSDMS limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.
- PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the Clinical Center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.3.2 Procedures for sample storage at the Clinical Pharmacology Program:

- Barcoded samples are stored in barcoded boxes in a locked freezer at either -20ºC or -80ºC according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in PSDMS. All researchers are required to sign a form stating that the samples are only to

be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

- Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.
- If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) that meet expedited reporting requirements (see section **7.2.1)** will be reported.
- Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.4 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.4.1 Description of the scope of genetic/genomic analysis

Tumor tissue and liquid biopsies (plasma, saliva) will be used for genomic analysis to identify somatic alterations. Blood will be used for "normal" DNA isolation and sequenced to identify somatic alterations. Whole exome, transcriptome, whole genome and/or targeted NGS will be performed in the DNA/RNA isolated from these specimens.

5.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

Tissue and blood samples collected will be coded and linked. DNA, RNA and protein isolated from these tissues and cell lines and xenografts generated will all be similarly coded. Only personnel involved in this study will have access to both the code and the name of the patient. Coded, linked tumor tissue will be sent to collaborator, Dr. Christopher Albanese, at Georgetown University for generating cell lines. All samples will be coded and linked without any patient identifiers and the Georgetown investigators will have no access to patient identification.

To facilitate genetic research, and for the purpose of publication of research work, data from genomic and proteomic studies may be deposited in appropriate public databases. Coded, linked data will be deposited in a manner that the patient's identity cannot be traced.

5.4.3 Management of Results

The analyses performed in various NCI laboratories under this protocol are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing for clinical purposes. Changes observed unrelated to our research may or may not be valid. Therefore, we do not plan to inform participants of the results of testing on the tissue, saliva and blood that is performed in our research lab.

However, in the unlikely event that clinically relevant incidental findings are discovered, subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects or their designee will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be referred to an NCI CCR Genetics Branch certified genetic health care provider for the disclosure of the results.

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

The costs of CLIA testing will be paid for by the Center for Cancer Research, the Branch, or the Principal Investigator. If the health history, family history, or tumor diagnosis from the Laboratory of Pathology at the NIH Clinical Center suggests that the participant might benefit from genetic testing, we will discuss this with him/her.

At the time of consent, subjects will be informed that incidental genetic findings may arise from this study. Participants will be asked complete and sign an NIH-527 Release form at the time of consent. The completion of the form is optional, but a note will be made in the medical record to document refusal. In the event that the participant dies or becomes incapacitated in the time frame between providing a sample for germline analysis and results being available, results will be provided to the individual specified on the release form.

5.4.4 Genetic counseling

Should any incidental findings be discovered, the NCI CCR Genetics Branch will be asked to provide genetic counseling. In the event a result of urgent importance to immediate family members has to be divulged, family members will be offered genetic counseling.

5.5 WITHDRAWAL OF INFORMED CONSENT FOR DONATED BIOLOGICAL SAMPLES

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. The participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved. If samples are already analyzed, the PI is not obliged to destroy the

results of this research. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into the in-house password protected electronic systems, C3D and LabMatrix, and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study drug administration, C1D1, until 30 days after the last dose is given. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

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.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per the requirements in section **7.2.1**.

The following data will be collected:

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_**X**_ Coded, linked data in an NIH-funded or approved public repository.

___ Coded, linked data in another public repository.

_**X**_ Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

_**X**_ Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_**X**_ An NIH-funded or approved public repository. Insert name or names:____clinicaltrials.gov; dbGAP.

_**X**_ BTRIS (automatic for activities in the Clinical Center)

_**X**_ Approved outside collaborators under appropriate individual agreements.

_**X**_ Publication and/or public presentations.

When will the data be shared?

_**X**_ Before publication.

_**X**_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[67] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Definitions

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

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.

6.3.2 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:

- By chest x-ray: ≥20 mm
- By CT scan:
    - Scan slice thickness 5 mm or under: ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

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/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Post-LAT Lesions

Progression: As defined in Section 4.3.1 of the RECIST version 1.1 manuscript[69], at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Note: If patients progress only at the same site where LAT has been performed before, the progression will be considered to be a result of inadequate ablation and they will be considered for repeat LAT if clinically feasible by any of the previous modalities (surgery, RT, RFA, cryoablation) and again re-challenged with osimertinib. Progression only at the site of previous LAT will not be considered progression for the PFS2. Re-initiation of osimertinib treatment in this case has to be within one month.

6.3.3 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.

RECIST criteria will be used to determine disease progression unless there is cytological or histological confirmation of an alternative diagnosis such as pneumonia or inflammation. At the time of first progression when a biopsy is mandatory, biopsy will confirm disease progression. For instances of second progression when a biopsy is not mandatory, progression determined using RECIST criteria will be adequate to take patient off treatment.

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.

6.3.4 Response Criteria

6.3.4.1 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.

6.3.4.2 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).

6.3.4.3 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 4. Evaluation of patients with measurable 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 5. Evaluation of patients with non-measurable 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

6.3.5 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.

6.3.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.3.7 Overall Survival

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

6.4 SAFETY ASSESSMENTS

6.4.1 Laboratory safety assessments

Blood for determination of clinical chemistry, hematology and coagulation will be taken at the times indicated in the **Study Calendar**. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

Please refer to section **2.3** for the list of laboratory variables assessed.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section **6.4.1** and section **7.**

In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to **Appendix E** 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.4.2 Physical examination

A physical examination will be conducted at screening and at subsequent visits according to the schedule in section **3.6**.

6.4.3 ECG

Patients should be monitored for ECG changes according to the schedule in section **3.6** ECGs should be reviewed and any abnormalities noted.

6.4.3.1 Resting 12-lead ECG

Twelve-lead ECG will be obtained after the patient has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study if possible.

The investigator or designated physician will review the ECG and may refer to a cardiologist if appropriate. A paper copy should be filed in the patient's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs, ECG intervals and an overall evaluation will be recorded.

6.4.4 Ophthalmologic exam

Full ophthalmic assessment, including slit lamp examination, should be performed at screening and if a patient experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated. Ophthalmology examination results should be collected in the eCRF.

Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an AE. Photographs should be performed to record any clinically significant findings.

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research event found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

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7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical

Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at dahutw@mail.nih.gov and to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. All data will be collected in a timely manner and reviewed by the principal investigator or the lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATOR

The PI or designee will send all reports to the manufacturer as described below.

8.1.1 Expedited Adverse Event Reporting Criteria to the IND Manufacturer

Any serious or unexpected adverse events occurring from the start of treatment until 30 days after the last dose of study medication will be faxed or emailed to AstraZeneca at the time the event is discovered. The PI or designee should send reports to jennifer.defrancisco@astrazeneca.com and AEMailboxClinicalTrialTCS@astrazeneca.com.

* A ***cover page*** (see **Appendix F**) should accompany the ***MedWatch*** form indicating the following:

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

* The 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 the SUSAR report and accompanying cover page by way of fax or email to AstraZeneca's designated fax line or by email as listed on the cover page in Appendix F***

8.1.2 Additional Information Sent to AstraZeneca

The following items must be provided to AstraZeneca:

1. IRB approval of initial protocol
2. Any other information affecting the safety of human subjects research conducted under the CTA.
3. Quarterly Reports Entered into the AstraZeneca Database
    a. Cumulative frequency table of adverse events in a table listing event name and CTC grade
    b. Number of subjects screened, enrolled, completed, withdrawn

Unless otherwise indicated, the information should be sent to by email to Jennifer DeFrancisco, Jennifer.defrancisco@astrazeneca.com

9 CLINICAL MONITORING

Although this study is IND-exempt, the CCR will maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL CONSIDERATIONS AND SAMPLE SIZE ESTIMATE

The primary objective is to determine PFS in patients with oligoprogressive disease after treatment with LAT followed by osimertinib. Patients who progress on their initial treatment with osimertinib and receive LAT therapy (surgery, radiation therapy, RFA, or cryoablation) followed by osimertinib will be evaluated for their time to second progression (PFS2). The objective will be to estimate the PFS2 for these patients and also to determine if the PFS2 results may be potentially superior to the expected results. Data from a recently published study indicated that patients with NSCLC who have progressed after receiving LAT would be expected to have approximately a 6.2 month median PFS2. With 41 evaluable patients receiving LAT, assuming accrual would take place over approximately 3 years, and that there

would be at least 6 months of additional potential follow-up after the last patient has received the LAT followed by osimertinib , there would be 80% power to determine that there is a difference between a 6 month median PFS and an improved 10 month median PFS, with a one sided 0.10 alpha level test, using the method of Brookmeyer and Crowley as calculated via the following website: http://www.swogstat.org/stat/public/one_nonparametric_survival.html.

The trial also aims to better define PFS in patients with *EGFR* mutation-positive NSCLC treated with osimertinib prior to LAT. Data from recently published studied indicated that patients with T790M-positive EGFR inhibitor-resistant NSCLC experienced a median 9.6 month PFS following osimertinib treatment and 83% of patients treated with osimertinib at a dose of 80 mg daily as a first-line treatment remained progression-free at 9 months. Using a combined population of patients who are chemo-naïve or who had progressive disease after prior EGFR-TKI therapy, the present trial aims to treat both cohorts of patients with osimertinib in order to replicate the findings and to report the results in the two populations.

In order to obtain 41 patients who receive LAT followed by osimertinib, it is anticipated that at least 100 patients would need to enroll onto the trial and receive treatment initially with osimertinib. These patients will all be followed for PFS and will have their initial PFS reported in an overall group as well as separately by prior treatment status (TKI naïve vs. prior 1st or 2nd generation EGFR TKI treatment). In order to recruit patients fast for the evaluation of LAT and re-treatment with osimertinib, a cohort of patients already treated with osimertinib in other institutions in on-going clinical trials and developed acquired resistance will be included in the trial. These patients will be enrolled in this study if they are eligible for LAT and be followed for PFS after LAT and re-treatment with osimertinib.

In order to ensure that the trial does not continue to enroll patients in the event that outcomes are not adequate the following stopping rules will be implemented. For the patients initially receiving osimertinib on the trial, the initial median PFS would be expected to be approximately 9.6 months, with a lower two-sided 95% confidence interval bound of approximately 8.3 months. After 50 patients have been treated with osimertinib and potentially followed for at least one year, if the median PFS is below 8.3 months, then no further patients will be treated on the trial since the results associated with the first administration of osimertinib are substantially below what would be expected based on the previous study.

For the patients who receive LAT, based on results from the prior published study, the median PFS would be 6.2 months, with a lower two-sided 95% confidence interval bound of 3.7 months. If after 20 patients on the present trial have received LAT followed by osimertinib and were followed for a potential of 9 months, the median PFS is 3.7 months or less, then no further patients will be enrolled on the trial since this would indicate results which are substantially below what would be expected based on the previous study.

As re-treatment is allowed on this study, first treatment and second treatment patients will be included in the analysis of PFS as patients will not have been off osimertinib more than 1 month. Response criteria will be also assessed for both treatments as part of the analysis.

In order to obtain 41 evaluable patients who receive LAT followed by osimertinib, the trial will have an initial accrual ceiling of 100 patients. When appropriate, based upon the fraction of all patients who are able to receive LAT, the trial will be amended to request additional patients expected to be necessary to result in 41 evaluable patients receiving LAT and osimertinib. It is

anticipated that 3 to 5 years may be required to enroll adequate patients to obtain 41 who will receive LAT.

10.2 METHODS FOR STATISTICAL ANALYSES

The progression-free survival of patients with oligoprogressive disease after treatment with LAT followed by osimertinib will be estimated and plotted by the Kaplan–Meier method. In addition, the median progression-free survival will be reported along with the 95% confidence intervals. The results for the patients who undergo LAT are not expected to vary substantially according to whether they were initially EGFR TKI-naïve or not. However, the results will be evaluated including all patients who receive LAT as well as divided according to their initial EGFR TKI experience before treatment on this trial. The progression-free survival of patients treated with osimertinib prior to LAT will be estimated by the Kaplan-Meier method.

Other important objectives include evaluating responses and overall survival (OS) in the patients who receive osimertinib after LAT, as well as determining the feasibility of evaluating *EGFR* mutation status using liquid biopsies (using blood or saliva samples). The response rate will be reported using a 95% confidence interval and OS will be reported using a Kaplan-Meier curve. The percentage of positive *EGFR* mutation in blood or saliva samples will be reported and the sensitivity and specificity of liquid biopsies will be assessed.

Except for the evaluation of PFS2 in patients with oligoprogressive disease after treatment with LAT followed by osimertinib for which a one-sided 0.10 evaluation will be performed, all statistical tests will be two-sided and considered statistically significant when the p-value is <0.05. All statistical analyses will be performed using SAS (Version 9.4; SAS Institute, Cary, NC).

11 COLLABORATIVE AGREEMENTS

11.1 CLINICAL TRIAL AGREEMENT

A Clinical Trial Agreement (CTA # 990-16) with AstraZeneca was executed on 02/05/2016 for the clinical development of AZD-9291.

11.2 MATERIAL TRANSFER AGREEMENTS

Human Materials Transfer Agreements with the following collaborators have been obtained or will be obtained prior to sending materials from NCI.

1. Parker Cassidy at Mitra Biotech in order to perform the studies described in Section **5.1.1.3**
2. Dr. David Wong's group at UCLA in order to perform the studies described in Section **5.1.3**
3. Dr. Christopher Albanese at Georgetown University in order to perform the studies described in Section **5.4.2**.
4. Dr. Amit Chaudhuri at Medgenome to perform the studies described in Section **5.1.1.3.10**.

5. Dr. Julia Beaver and Dr. Elliot Rosen at the Food and Drug Administration in order to perform the studies described in Section **5.1.1.5**.
6. Dr. Olga Vitek at Northeastern University in order to perform the studies described in Section **5.1.1.3.5**.
7. Dr. Greg Jones at Inivata in order to perform the studies described in Section **5.1.1.4**.
8. Dr. Haixu Tang at Indiana University to perform the studies described in Section **5.1.1.7**.
9. Drs. James Sun and Jennifer Busby at Gritstone Oncology to perform the studies described in Section **5.1.1.8**.

11.3 Cooperative Research and Development Agreement

A Materials Cooperative Research and Development Agreement (CRADA) #03288 with Aurigene was executed on 05/06/2019 and includes experiments described in the Experimental Plan - Section 5 which involve the use of patient-derived xenograft mouse models under this clinical protocol.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one sex, racial or ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

This study will be recruited through internal referral, our local physician referral base, and through various websites (i.e., clinicaltrials.gov).

12.2 Participation of Children

Patients under the age of 18 will be excluded from study due to the low occurrence of these oncologic histologies in the pediatric population. In addition, the risk of exposure to an investigational agent without proven benefit in the targeted histologies supports excluding children until additional safety and efficacy data is available.

12.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **12.4.2**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated

or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

12.4.1 Risks

12.4.1.1 Risks of study therapy

Potential risks include the possible occurrence of any of a range of side effects that are listed in section **13.1.2** and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier.

12.4.1.2 Non-physical risks of genetic research

12.4.1.2.1 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded investigational and will not be shared with patients, family members or health care providers.

12.4.1.2.2 Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

As part of study efforts to provide confidentiality of subject information, this study has obtained a Certificate of Confidentiality which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

12.4.1.3 Risks of biopsy

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, local anesthesia will be used. Rarely, there is a risk of infection at the sampling site. Lung biopsies also present the risk for pneumothorax. Tumor biopsies will be done only if it is clinically safe and feasible. In addition, as up to 3 research biopsies may be collected under CT

guidance, this will result in exposure to approximately 2.4 rem. This amount is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

12.4.2 Benefits

Taken together, benefits of combining osimertinib and local ablative therapy outweigh risks associated with the treatment. Patients should realize that we are hopeful that they may gain benefit from this study, but there is no objective evidence to support our optimism at this time. The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or survival.

12.5 CONSENT PROCESS AND DOCUMENTATION

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study. The informed consent process will be documented on a progress note by the consenting investigator.

12.5.1 Telephone consent

For re-consent in the case of protocol amendments, the informed consent document may be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented in the medical record.

13 PHARMACEUTICAL INFORMATION

13.1 OSIMERTINIB (AZD9291)

Note: The commercial drugs used in this study will not alter labelling of the FDA approved drugs nor does the investigation involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. The FDA has determined that this protocol is IND exempt based on this.

13.1.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer

AZD9291 (osimertinib)	40mg Tablets 80mg Tablets	AstraZeneca

AstraZeneca will supply AZD9291 as tablets for oral administration as a single daily dose of 80 mg. AZD9291 will usually be supplied as either bulk or unlabeled bottles for ISS/ESR studies.

13.1.2 Toxicity

Based on the phase I study by Janne et al., most of the adverse effects were grade 1 or 2[33]. 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 interval; none of these events led to discontinuation or reduction of AZD9291. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate renal impairment as well as those with mild hepatic impairment[76]. Exploratory analyses of clinical trials of AZD9291 suggest a higher incidence of Grade 3 or 4 adverse reactions (32% vs. 25%) and more frequent dose modification for adverse reactions (23% vs. 17%) in patients 65 years or older as compared with those younger than 65 years[76]. Based on the two retrospective studies and one prospective study, it has been shown that local ablative therapies are well tolerated in combination with EGFR-TKI[56-58].

13.1.3 Administration Procedures

Osimertinib is administered as 80 mg once daily for patients without leptomeningeal disease and 160 mg per day for those with leptomeningeal disease at baseline. Osimertinib can be taken without regard to food. Doses should be taken approximately 24 hours apart at the same time point each day. Doses should not be missed. If a patient misses taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the dose time, the missed dose should not be taken, and patients should be instructed to take the next dose at the next scheduled time. If a patient vomits after taking their osimertinib, they should not make up for this dose, but should take the next scheduled dose.

If a patient misses more than 5 scheduled doses of osimertinib within one cycle, this will be reported as a protocol deviation. If a patient misses 1-4 doses of osimertinib within one cycle, this will not be considered a deviation. If instructed by the study team to hold the investigational drug, held doses will not be considered a missed dose. A patient that interrupts therapy for more than 4 weeks will be taken off treatment.

The dose of osimertinib can be reduced based on the rules described in Section **3.4**. Further dose reductions are not possible. Once a dose has been reduced, it should not be re-escalated at future cycles. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded.

Patients may continue to receive osimertinib as long as they are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

13.1.4 Formulation

Osimertinib is presented for oral administration as a beige, film-coated tablet containing either 40 mg or 80 mg of osimertinib (expressed as the free base). Osimertinib tablets are packed in high-density polyethylene (HDPE) bottles. Bottles are secured with a child resistant closure;

induction-sealed membranes provide tamper evidence.

13.1.5 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling.

13.1.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

13.1.7 Stability

The investigational product label on the bottle specifies the stability/expiration date.

13.1.8 Incompatibilities

As CYP3A4 is the principal P450 protein responsible for the metabolism of osimertinib, AZ5104 and AZ7550, co-administration with a potent CYP3A4 inhibitor or inducer may affect their exposure.

Osimertinib, AZ5104 and AZ7550 are substrates for P-gp and BCRP but are not substrates for OATP1B1 and OATP1B3.

Osimertinib is a direct inhibitor of CYP 3A4/5 *in vitro* using nifedipine as the probe substrate (IC50 5.1 μM) although lower inhibition was observed with midazolam (IC50 >26.5 μM) and is a weak time-dependent inhibitor of CYP3A4 *in vitro* (KI and kinact of 1090 μM and 0.0617 min-1). The exposure of medications dependent on CYP3A4/5 may be increased when coadministered with osimertinib.

Osimertinib is an inhibitor of BCRP *in vitro* (IC50 of 2.0 μM). The exposure of medications dependent on BCRP may be increased when co-administered with osimertinib due to BCRP inhibition.

Osimertinib induces CYP3A4 and CYP1A2 *in vitro* in human hepatocytes. The exposure of medications dependent on CYPs 3A4 and 1A2 (also CYP2C and P-gp which may be induced) may be reduced when co-administered with osimertinib.

13.1.9 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

14 REFERENCES

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15 APPENDICES

15.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

15.2 APPENDIX B. 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 eCRF.

Osimertinib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and predicted clinical exposure data, osimertinib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have shown that the principal CYP enzymes responsible for the Phase I metabolism of osimertinib are CYP2C8, CYP3A4, and CYP3A5.

1. DRUGS INHIBITING CYP3A4 OR CYP2C8 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH OSIMERTINIB

The contribution of Phase I metabolism to the total clearance of osimertinib is currently unknown but, to ensure patient safety, the following potent inhibitors of CYP3A4 should be avoided during this study if possible for any patient receiving osimertinib. If no alternative exists, the patient should be closely monitored for signs of toxicity.

Table 1. Drugs inhibiting CYP3A4

Contraindicated drugs	
Clarithromycin, telithromycin, troleandomycin Conivaptan Indinavir, lopinavir, nelfinavir, ritonavir, Itraconazole, ketoconazole, posaconazole, Mibefradil Nefazodone	Consider withdrawing 1 week prior to osimertinib start

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.

2. DRUGS INDUCING CYP3A4 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMEND ARE NOT COMBINED WITH OSIMERTINIB

The following potent inducers of CYP3A4 should be avoided during this study if possible for any patient receiving osimertinib because concomitant use may decrease osimertinib plasma concentrations.

Table 2. Drugs inducing CYP3A4

Contraindicated drugs	**start**
Carbamazepine, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentine	Consider withdrawing 3 weeks prior to

St John's Wort	osimertinib start
Phenobarbitone	Consider withdrawing 5 weeks prior to osimertinib start

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.

3. MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY OSIMERTINIB THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

Table 3. Exposure, pharmacological action and toxicity may be increased or decreased by osimertinib

Warning of possible interaction	**Advice**
Alfentanil Amodiaquine Repaglinide Sirolimus Tacrolimus Torsemide Fentanyl Dihydroergotamine Ergotamine Simvastatin Lovastatin Atorvastatin Rosuvastatin Fluvastatin Sulfasalazine Warfarin Phenytoin (also see Table 2) s-Mephenytoin Cyclosporine Theophylline Tizanidine Aliskiren Ambrisentan Colchicine	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.

Dabigatran etexilate

Digoxin

Fexofenadine

Maraviroc

Ranolazine

Talinolol

Tolvaptan

Maraviroc

Ranolazine

Talinolol

Tolvaptan

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and osimertinib; *in vitro* data suggest osimertinib has the potential to cause drug interactions at the intestinal level through CYP3A4 and BCRP, it has also been shown to be an inhibitor of CYP2C8 and inducer of CYP3A4, CYP1A2 and CYP2C and p-glycoprotein. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to depend on CYP3A4, CYP2C8, CYP1A2 and CYP2C for metabolism or BCRP and p-glycoprotein for deposition disposition. Appropriate medical judgement is required.

4. 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 and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm.

4.1. Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 4. Drugs prolonging QT interval

Contraindicated drug	**Withdrawal period prior to osimertinib start**
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 weeks

Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

4.2. **Drugs that may possibly prolong QT interval**

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Table 5. Drugs that may prolong QT interval

Drug	**Minimum treatment period on medication prior to osimertinib start**
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isradipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprim-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

15.3 APPENDIX C: OSIMERTINIB PATIENT MEDICATION DIARY

INSTRUCTIONS TO THE PATIENT:

1. Complete 1 diary for each 4-week (28-day) cycle of treatment.
2. You will take your dose of osimertinib once daily at around the same time. You may take it with or without food. You should take the tablet whole with water. The tablet should not be crushed, split or chewed.
3. Record the date, the number of osimertinib tablets you swallowed and the time you took the medicine.
4. Record the daily dose onto the diary, including missed, skipped, or vomited doses. If you vomit after taking the tablets, do not make up the dose, but take the next scheduled dose.
5. If you miss a dose of osimertinib and it is more than 12 hours after your usual dose time, the missed dose *should not* be taken, but take your next scheduled dose. If you miss taking a scheduled dose, within a window of 12 hours, it is acceptable to take the dose.
6. If you have any comments or notice any side effects, please write them in the comments column.
7. Please bring this diary and your bottle(s) of osimertinib when you return for each appointment.

Today's Date:_____ Cycle:_____ OSIMERTINIB Dose:_____

Patient Study ID:_____

DAY	DATE	TIME TAKEN	DOSE TAKEN	# OF TABLETS TAKEN	COMMENTS
1.					
2.					
3.					
4.					
5.					
6.					
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Patient Label

15.4 APPENDIX D. GUIDANCE FOR THE MANAGEMENT OF ADVERSE EVENTS IN STUDIES USING 80MG OSIMERTINIB

Osimertinib is a potent irreversible small molecule inhibitor of both the single EGFRm (tyrosine kinase inhibitor (TKI) sensitivity conferring mutations) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR, with weaker inhibition towards wild type EGFR.

Clinical experience with 80mg osimertinib has shown an association with the occurrence of dermatological adverse events (particularly rash and dry skin) and diarrhea. The considerable majority of these events have been mild, transient events that have not always required treatment.

Based on experience with other EGFR and HER2 inhibitors, decreases in LVEF, anterior ocular effects and ILD/pneumonitis should be monitored for.

Some guidance is provided in this document regarding these events.

The purpose of these treatment guidelines is:

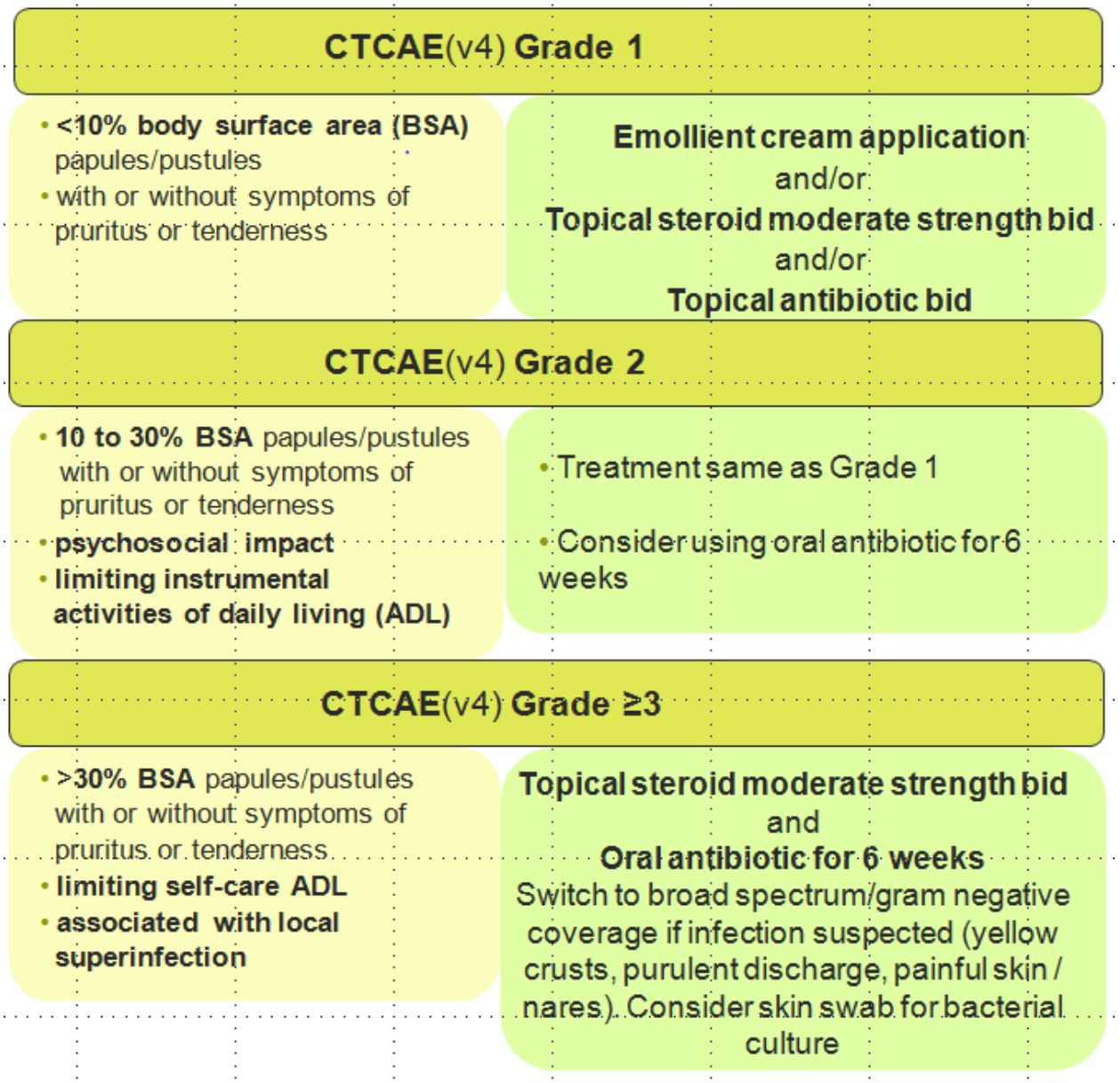
- To prevent tolerable adverse events becoming intolerable for the patient and leading to discontinuation of treatment.
- To promote consistency of treatment for specific adverse events across the osimertinib clinical program.

1. Skin Events – Rashes & Acnes, Dry Skin / Xerosis, Paronychia

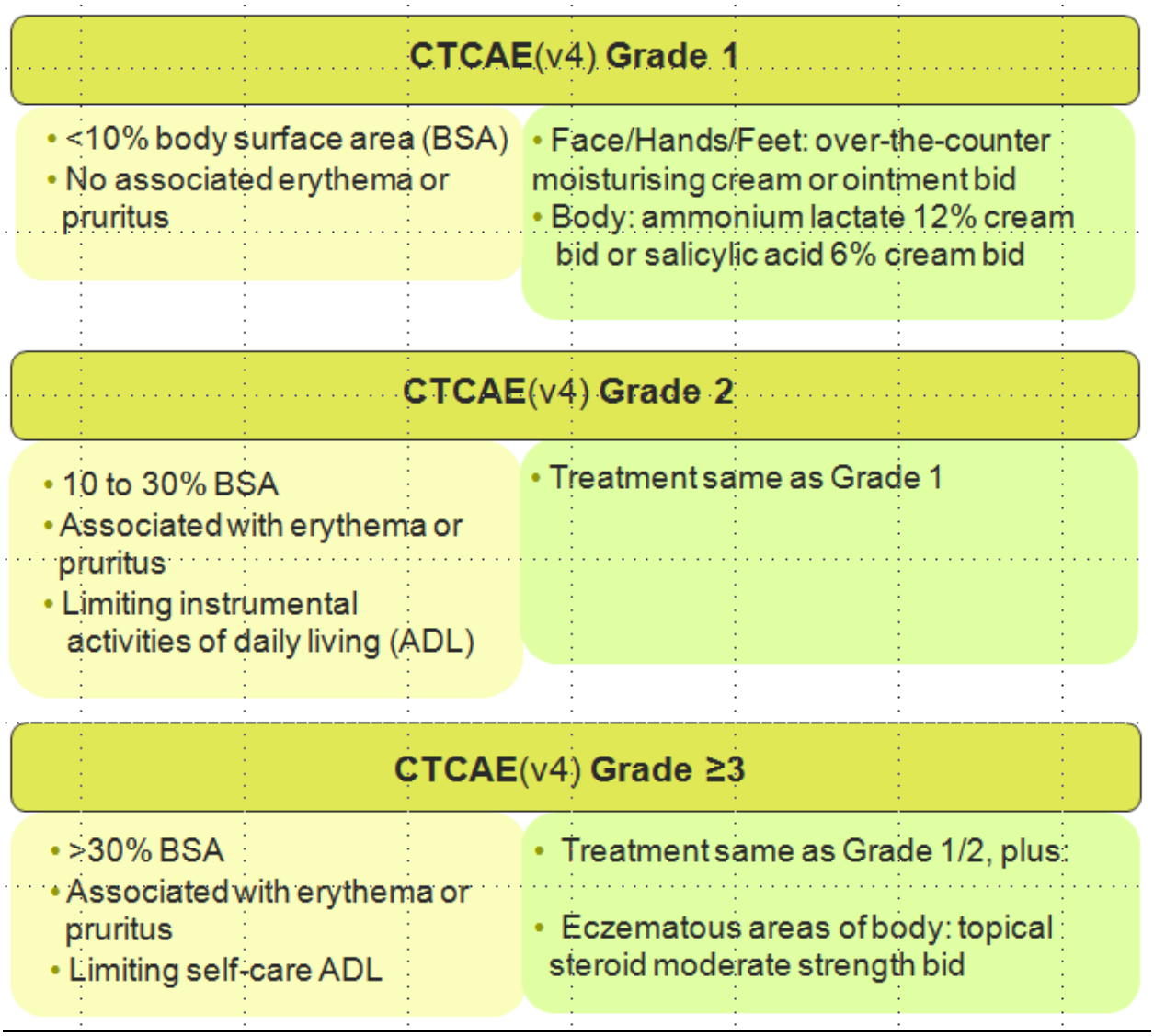
Patients may consider applying over-the-counter moisturising cream to face, hands and feet twice daily from the start of treatment with osimertinib.

Skin effects may occur at any time, but most likely to start within 2 weeks of starting treatment.

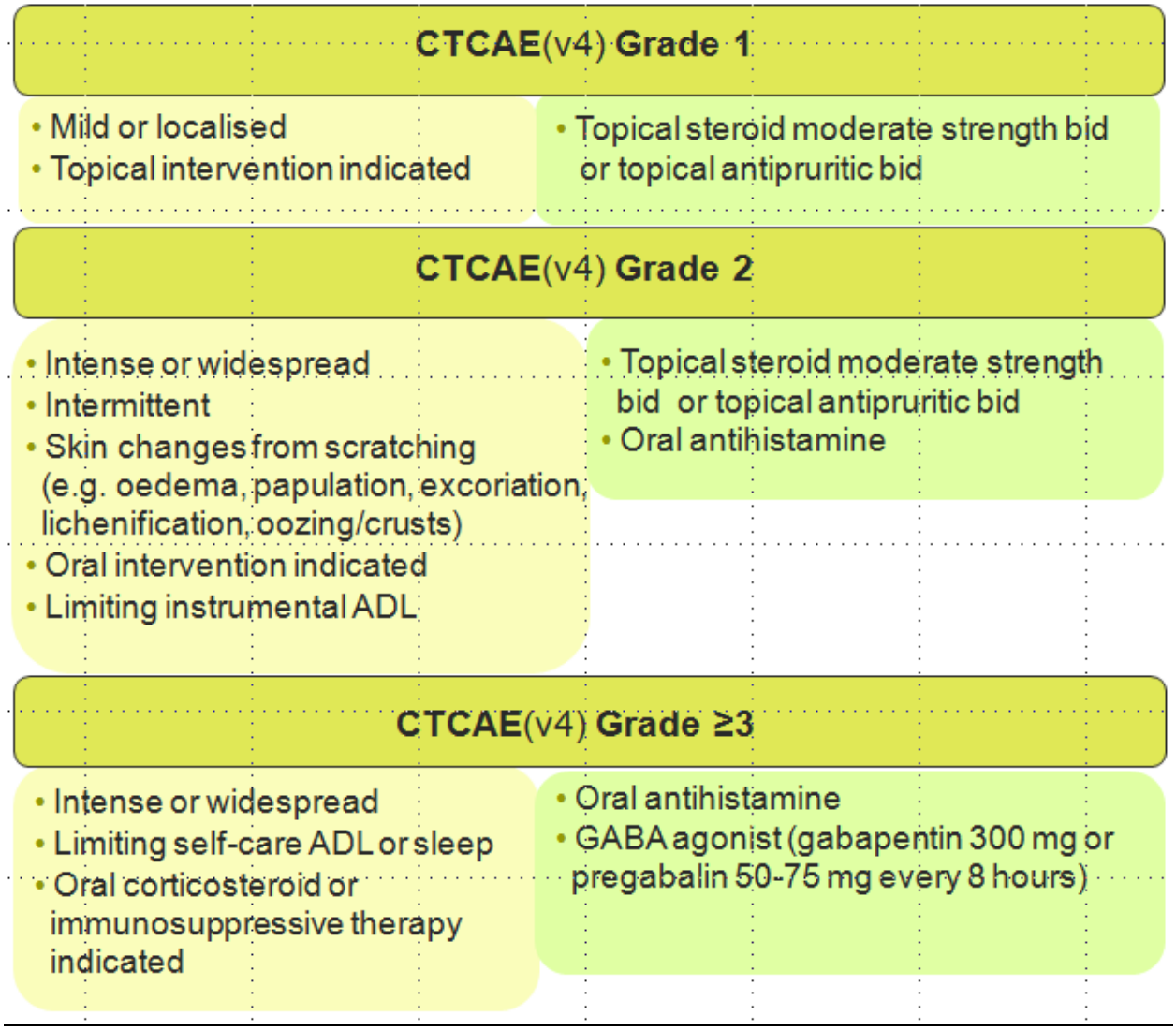
Rashes and Acne



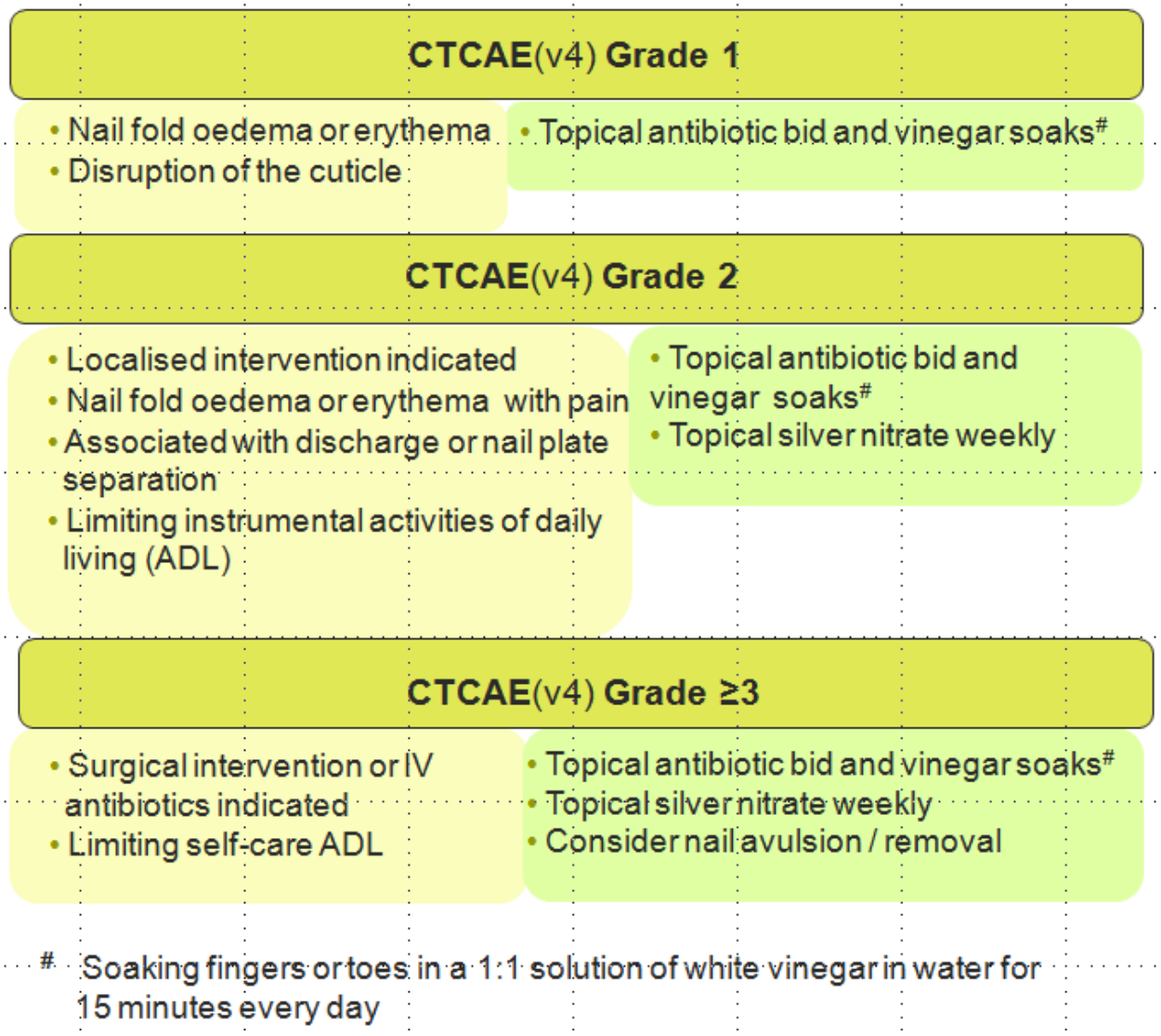
Dry Skin / Xerosis



Pruritis


CTCAE(v4) Grade 1
• Mild or localised
• Topical intervention indicated
• Topical steroid moderate strength bid or topical antipruritic bid
CTCAE(v4) Grade 2
• Intense or widespread
• Intermittent
• Skin changes from scratching (e.g. oedema, papulation, excoriation, lichenification, oozing/crusts)
• Oral intervention indicated
• Limiting instrumental ADL
• Topical steroid moderate strength bid or topical antipruritic bid
• Oral antihistamine
CTCAE(v4) Grade ≥3
• Intense or widespread
• Limiting self-care ADL or sleep
• Oral corticosteroid or immunosuppressive therapy indicated
• Oral antihistamine
• GABA agonist (gabapentin 300 mg or pregabalin 50-75 mg every 8 hours)

Paronychia

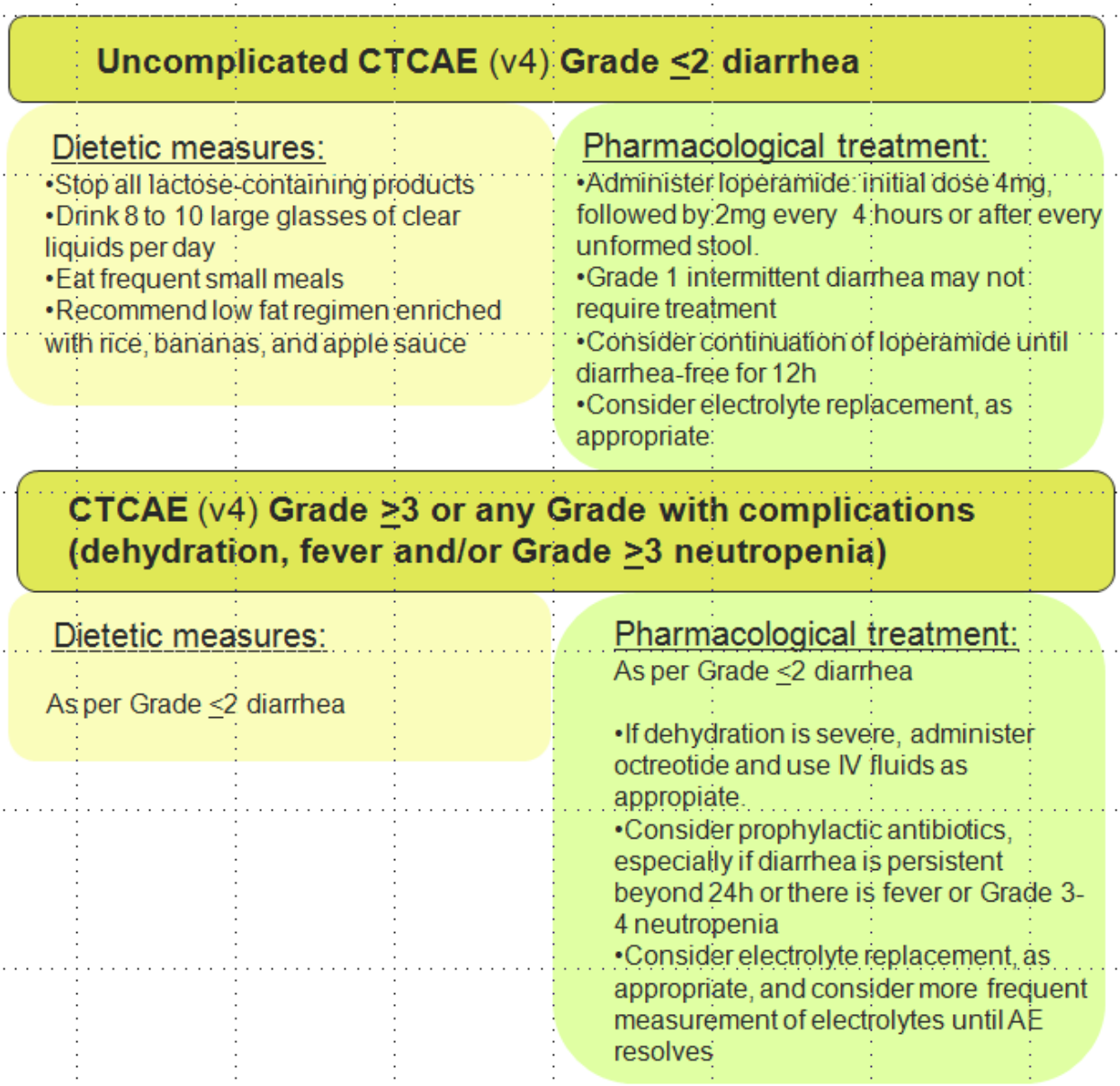


Dermatologic Guidance Summary:

- Patients may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of treatment.
- Physicians may consider issuing a prescription for topical treatment to patients. However, topical steroids and topical or oral antibiotics should not be implemented prophylactically and treatment should only be started when confirmed by the treating physician.
- As soon as an acneiform / papulopustular rash occurs, treatment with moderate strength topical steroids and antibiotics should be implemented.

- The occurrence of non-papulopustular skin reactions should be treated appropriately, as defined by the treating physician, and in consultation with a dermatologist where necessary
- Use of topical benzoyl peroxides and other irritating anti-acne agents should be avoided.
- Patients should be fully informed regarding skin reactions
    - may occur during treatment with osimertinib
        - skin reactions are not contagious, and
        - do not result from allergy to treatment
    - may consider applying over-the-counter moisturising cream to face, hands and feet bid from the start of treatment
    - to contact the study team to report any instances of skin reaction as soon as they arise so that appropriate treatment can be promptly initiated
        - and, especially if the skin reaction changes (e.g. if it spreads or becomes painful)
    - It may be beneficial to avoid irritating skin products (e.g. irritating soaps, products containing retinol or retinoic acid)
    - Camouflage make-up (non-comedogenic or non-pore blocking) can be used during treatment

2. Diarrhea Treatment Guidance



Diarrhea Guidance Summary:

- Patients should be fully informed regarding diarrhea
    - May occur during treatment with osimertinib
        - diarrhea is not contagious, and
        - does not result from allergy to treatment
    - Contact the study team to report any instances of diarrhea as soon as they arise so that appropriate treatment can be promptly initiated

3. Ophthalmic Guidance

There is a known association between the use EGFR TKIs and the occurrence of ophthalmic adverse events.

Patients on EGFR TKIs, including osimertinib, should be

- Fully informed that ophthalmic events may occur during treatment with osimertinib
- Monitored periodically for these events
- Osimertinib should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.
- Encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated. Symptoms may include:
    - Burning / itching / irritation / smarting
    - Redness with / without discharge
    - Blurred vision
    - Light sensitivity

Patients who wear contact lenses must discontinue wearing them if

- They have any mild to moderate eye symptoms (CTCAE grade ≤2) until at least one week after symptoms have resolved.
- Patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events until at least one week after treatment with osimertinib is permanently discontinued.

Patients must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by treating physician, at any time during the study until 1 week after osimertinib has been permanently discontinued.

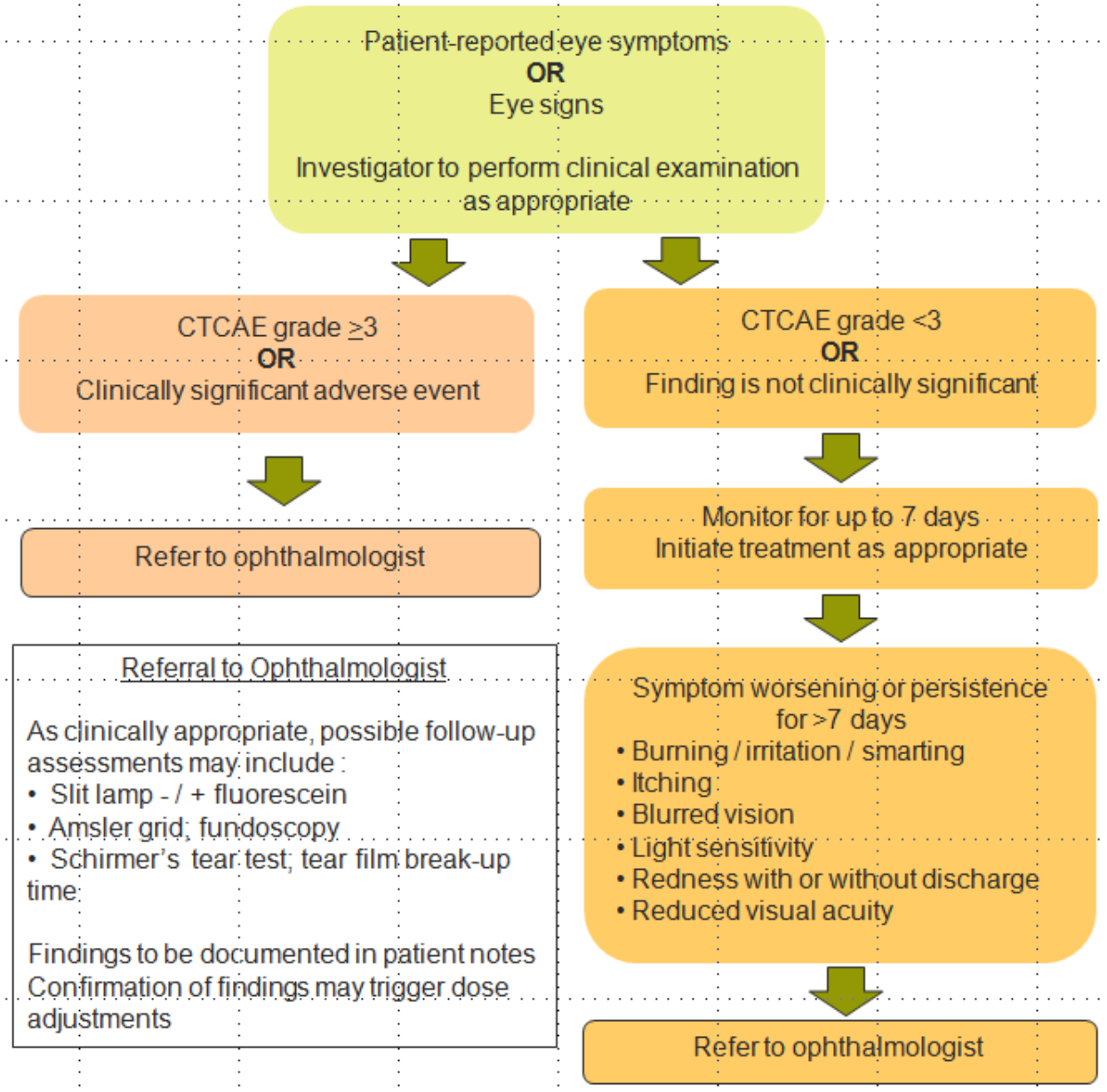
Assessments During Treatment

- If the patient reports any eye symptoms during treatment with osimertinib or if signs are observed during a study visit, the Investigator should perform a clinical examination including a best corrected near and distant visual acuity assessment as appropriate
- Findings should be documented in the patient's notes

Referral to Ophthalmologist

Patients with ophthalmic AEs of CTCAE Grade > 3 or eye symptoms that are clinically significant and/or persistent (>7 days) should be referred to the ophthalmologist. For example:

- Deterioration in near or distant visual acuity by more than one level
- Persistence or worsening of:
    - Burning/ irritation/ smarting
    - Light sensitivity (photophobia)
    - Itching
    - Blurred vision
    - Redness with or without discharge



Ophthalmic Dose Adjustments

Confirmed CTCAE Grade ≥3

OR

Clinically significant or persistent
(present for >7 days) event

AND

Considered causally related to osimertinib

Initiate ophthalmic treatment as appropriate and withhold dose for up to 4 weeks

- If event improves to CTCAE Grade ≤1 within 4 weeks, reinstate osimertinib at the current dose maintaining ophthalmic treatment as appropriate
- If event improves to CTCAE Grade 2 within 4 weeks, consider reinstating osimertinib at reduced dose of 40 mg daily, maintaining ophthalmic treatment as appropriate
- Permanently discontinue osimertinib and maintain ophthalmic treatment as appropriate, where
    - CTCAE Grade ≥3 or clinically significant or persistent adverse event does not improve to a lower CTCAE Grade within 4 weeks of osimertinib interruption, OR
    - Any ulcerative event

Ophthalmic Guidance Summary

- It is important that patients are fully informed that ophthalmic events may occur during treatment with osimertinib.
- Osimertinib should not be administered on the first scheduled day if the patient has any clinically significant eye symptoms.
- Patients should be encouraged to report any instances of ophthalmic symptoms and/or vision changes to allow the appropriate treatment to be initiated (or ophthalmic referral).
- Patients who wear contact lenses must discontinue wearing them if
    - They have any mild to moderate eye symptoms (CTCAE grade ≤2) until at least one week after symptoms have resolved.
    - Patient has a recurrence of eye symptoms or experiences any severe (CTCAE grade ≥3) ocular events until at least one week after treatment with osimertinib is permanently discontinued.
- Patients must not use any eye drops or ointment for treatment of eye symptoms, unless

agreed by a study doctor, at any time during the study until 1 week after osimertinib has been permanently discontinued

- Osimertinib dose should be interrupted, modified or permanently discontinued as appropriate for any ophthalmic events

4. Left Ventricular Ejection Fraction (LVEF)

Osimertinib and its active metabolite may also inhibit HER2. For this reason:

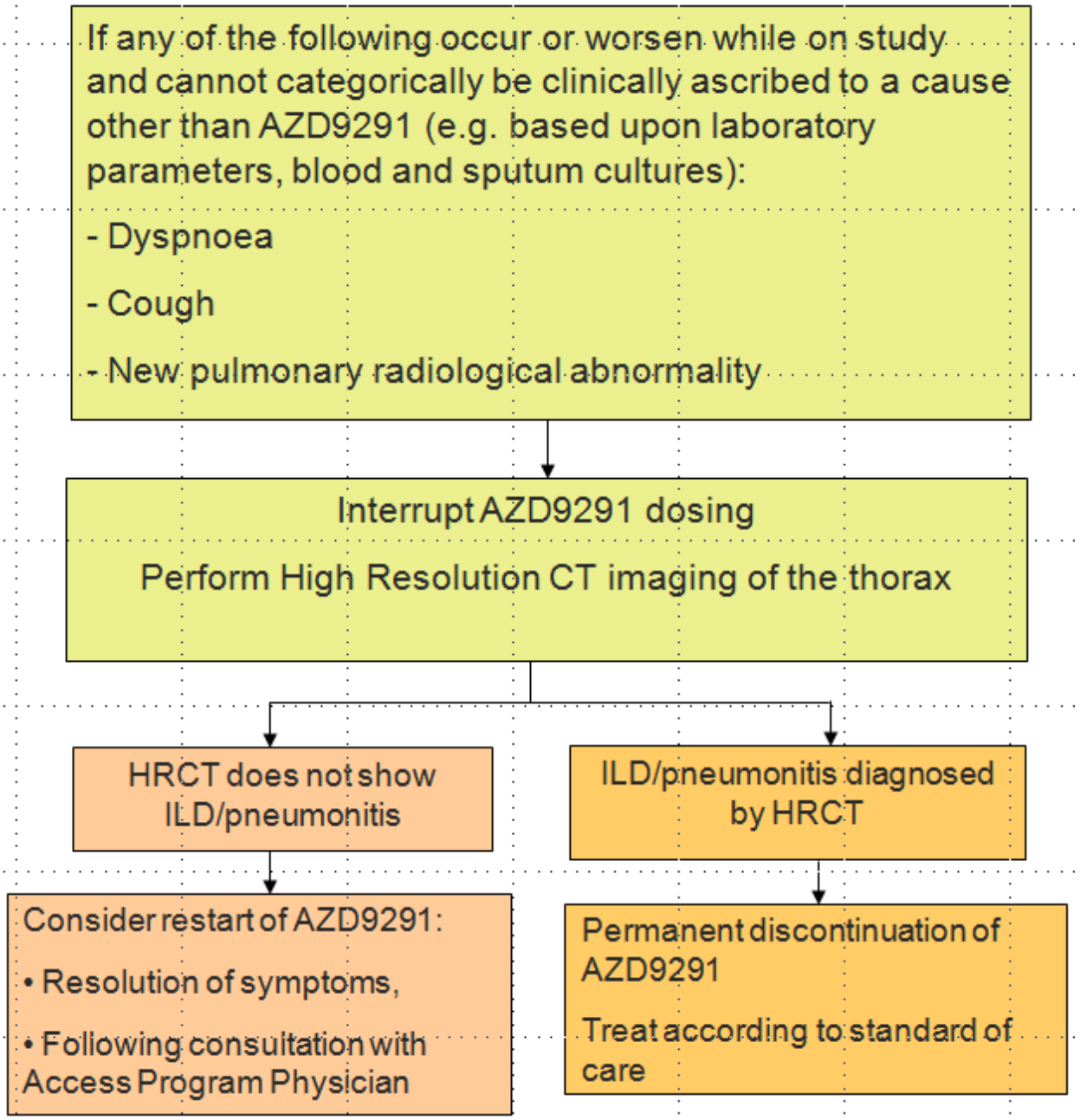
- Measurement of LVEF should be performed if the investigator has clinical suspicion of new onset impaired cardiac function
- Patients are to be managed clinically according to standard of care

5. Interstitial Lung Disease (ILD) / Pneumonitis Guidance

If you have clinical suspicion of interstitial lung disease (ILD), dosing with osimertinib should be interrupted while further investigations are performed.

A diagnostic workup (including HRCT, blood and sputum culture, laboratory parameters) should be performed, to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage.

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.



ILD / Pneumonitis Guidance Summary

- Interrupt osimertinib dosing, if you have clinical suspicion of interstitial lung disease (ILD), while further investigations are performed.
- Perform full diagnostic workup (including HRCT, blood and sputum culture, laboratory parameters to exclude conditions such as lymphangitic carcinomatosis, infection, allergy or pulmonary haemorrhage
- Contact the Medical Lead as soon as a potential pneumonitis event is identified.
- Complete and submit pneumonitis questionnaire

- Resume osimertinib dosing as appropriate

6. Summary

- Patients should be fully informed of common adverse events associated with EGFR TKIs, including AZD921. Counselling should include
  - Important aspects of preventative self-care measures
  - When to notify physician of symptoms that may require further evaluation or treatment
  - Appropriate treatments associated with EGFR TKIs adverse events
  - Importance of osimertinib dosing adherence or the importance of dose holds or reductions when appropriate
- Physicians should do the following:
  - Review the protocol and all associated documents provided by the study team
  - Familiarize themselves with the clinical management of EGFR TKI toxicity and required reporting as outlined in study documents

15.5 APPENDIX E. POTENTIAL DRUG INDUCED LIVER INJURY

1. INTRODUCTION

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator assesses cases meeting PHL criteria to determine whether Hy's Law (HL) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

2. DEFINITIONS

Potential Hy's Law (PHL)

A Potential Hy's Law (PHL) case is defined as a study patient with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

An HL case is defined as a study patient with an increase in serum AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, e.g., elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will, without delay, review each new laboratory report and if the identification criteria are met, will:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

4. FOLLOW-UP

4.1. Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria, the Investigator will:

• Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2. Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

• Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6).

The Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations.
- Complete the three Liver eCRF Modules as information becomes available.
- If at any time the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

The Investigator will follow the instructions below.

If there **is** an alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Record an SAE (report term 'Hy's Law').
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

6. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable to patients who meet PHL criteria on study treatment (including the 30 day follow-up period post discontinuation of study treatment) after having previously met PHL criteria at a study visit prior to starting study treatment.

At the first 'on-study treatment' occurrence of PHL criteria being met, the Investigator will:

Determine if there has been a significant change in the patient's condition compared with the last visit where PHL criteria were met:

- If there is no significant change, no action is required.
- If there is a significant change, follow the subsequent process described in Section 4.2 of this Appendix.

A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, and/or eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment (including the 30-day follow-up period) and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease or did the patient meet PHL criteria prior to starting study treatment and at their first 'on-study treatment' visit as described in Section 6?

If No: Follow the process described in Section 6 of this Appendix.

If Yes: Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Section 4.2 of this Appendix.

A 'significant' change in the patient's condition refers to a subsequent clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, and/or eosinophilia. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

8. **REFERENCES**

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

15.6 APPENDIX F. ASTRAZENECA SAE REPORT COVER SHEET

US ESR SAE REPORT COVERSHEET

Date:	
To:	AZ Patient Safety - TCS
Fax #:	1-302-886-4114
Email:	Jennifer.defrancisco@astrazeneca.com and AEMailboxClinicalTrialTCS@astrazeneca.com
Senders Name:	
Total number of pages: (including cover page)	

D-code:	
ESSROS Number:	
Sponsor Investigator/Site:	
Protocol Title:	
Initial or Follow Up:	

Message: