SUMMARY OF CHANGES

Date: March 9, 2018

Document: NCI Protocol #9878, PhI-80: "A Phase 1/2 Trial of Erlotinib and Onalespib lactate in EGFR-Mutant Non-Small Cell Lung Cancer."

Note: The following is a Summary of Changes between the 11.29.17 and 3.9.18 versions of the protocol

Section	Description of Change
Face Page	Updated protocol version in header and added new version date March 9, 2018 to protocol history. Updated California Cancer Consortium email address.
TOC	Updated page numbers.
5.2 and 7	Updated to CTCAE 5.0.

Recommendations from last amendment:

Section	Description of Change
4.3.3	The helpdesk number listed below is incorrect. Please update as per the below information: OPEN/IWRS Questions? Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: ~~609-619-7802 or~~ 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com. **PI Response:** DONE
4.1	**Please revise as shown below:** Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm ~~TBD~~>. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >. **PI Response:** DONE

NCI Protocol #: 9878

Local Protocol #: PhI-80

ClinicalTrials.gov Identifier: NCT02535338

TITLE: A Phase 1/2 Trial of Erlotinib and Onalespib lactate in EGFR-Mutant Non-Small Cell Lung Cancer

Corresponding Organization: **LAO-CA043** / City of Hope Comprehensive Cancer Center LAO
1500 E. Duarte Road, Duarte
California 91010
Phone: 626-256-HOPE(4673), extension 65928
Fax: 626-256-8654
Email: ccc@coh.org

Principal Investigator: Jonathan Riess, MD, MS
UC Davis Comprehensive Cancer Center
4501 X Street, Suite 3016
Sacramento, CA 95817
Phone: (916) 734-3772
Fax: (916) 734-7946
Email: jwriess@ucdavis.edu

Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

Statistician: Jeffrey Longmate, PhD
City of Hope
1500 E. Duarte Road
Duarte, CA 91010
Telephone: 626-256-8654
E-mail: jlongmate@coh.org

NCI-Supplied Agent(s): OSI-774 (erlotinib, NSC 718781)
Onalespib (onalespib lactate, AT13387, NSC 749712)

Other Agent(s): N/A

IND #:

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

July 29, 2015	Initial Protocol
August 26, 2015	Consensus Review
November 6, 2015	Amendment
December 4, 2015	Amendment
February 25, 2016	Amendment
August 15, 2016	RRA Amendment
March 2, 2017	Amendment
June 2, 2017	RRA Amendment
July 18, 2017	RRA Amendment
August 7, 2017	Amendment
November 29, 2017	Amendment
March 9, 2018	Amendment

SCHEMA

Stage IV NSCLC harboring an EGFR activating mutation with progressive disease by RECIST 1.1 on EGFR-TKI or EGFR-Exon 20 insertion with progressive disease on platinum containing chemotherapy.

↓

Phase 1 Dose Escalation of Erlotinib and AT13387 to determine the RP2D
(Each cycle is 28 days)

↓

Dose Level	Erlotinib (Oral, Daily)	ONALESPIB (IV, weekly D1, D8, D15)
-1	150 mg	120 mg/m2
0 (Starting)	**150 mg**	**150 mg/m2**
+1	150 mg	180 mg/m2
+2	150 mg	220 mg/m2

Phase 2 Cohort A (Closed as of 10/11/17)

Patients with Stage IV or recurrent/metastatic NSCLC that harbor an EGFR activating mutation (Exon 21 L858R, Exon 19 deletion, Exon 18 G719X, Exon 21 L861Q), age ≥18, without a complete or partial response on erlotinib as defined by RECIST 1.1 criteria after a minimum of 12 weeks on erlotinib; patients must be enrolled within 6 months of initiation of erlotinib

Phase 2 Cohort B (Open as of 10/11/17 and open to all ETCTN sites)

Patients with Stage IV or metastatic/recurrent NSCLC that harbor an EGFR exon 20 insertion and have progressive disease on or after platinum based chemotherapy.

Each Phase 2 cohort will be evaluated using Simon's two-stage minimax design, to detect a 25% RECIST response rate against an assumed background of 5%, with 10% type I and II error rates. The initial stage will enroll 13 subjects, continuing if one or more respond, with three or more out of 20 regarded as encouraging for further development.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- The primary objective of the phase 1 portion of this study is to determine the safety and tolerability of erlotinib and onalespib in patients with EGFR-mutant NSCLC.

- The primary objective of the phase 2 Cohort A is to preliminarily assess efficacy of combination erlotinib and onalespib at the RP2D determined in the phase 1 portion of the study in EGFR-mutant NSCLC patients who have not had a complete or partial response by RECIST 1.1 to frontline erlotinib after a minimum of 12 weeks on erlotinib. Patients must be enrolled within 6 months of initiation of erlotinib.

- The primary objective of the phase 2 cohort B is to preliminarily assess efficacy of combination erlotinib and onalespib at the RP2D in NSCLC patients whose tumor harbors an EGFR Exon 20 Insertion (an EGFR mutation not typically responsive to single agent erlotinib).

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity (primary aim phase 2, secondary aim phase 1). Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.2 To evaluate in a preliminary manner the progression-free survival (PFS) and disease control rate (DCR) of patients treated with erlotinib/ onalespib.

1.2.3 To characterize the pharmacokinetics of the above drug combinations at the recommended phase 2 dose (RP2D).

1.3 Exploratory Objectives

1.3.1 To explore plasma EGFR-mutant DNA as a biomarker by detecting changes in plasma EGFR-mutant DNA levels (including plasma EGFR-T790M) and new mutations that may represent resistance to treatment.

1.3.2 To demonstrate knockdown of Hsp90 client oncoproteins via treatment with erlotinib and onalespib by multiplexed immunofluorescence in serial tumor biopsies.

1.3.3 To establish patient derived xenotransplant models in EGFR-mutated NSCLC with a focus on tumors that lack response to single agent erlotinib and in patients with tumors harboring EGFR exon 20 insertions.

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer deaths worldwide due to the majority of patients presenting with metastatic disease for which there is no cure. In recent years, advances in the systemic treatment of non-small cell lung cancer (NSCLC) have increased survival by several months and subsets of patients enjoy prolonged survival beyond two years including patients with metastatic EGFR-mutant NSCLC[1]. More efficacious therapies have been a direct result of our increased understanding and exploitation of the molecular basis of lung cancer.

Platinum doublet chemotherapy has been the mainstay of NSCLC treatment with median OS of about 12 months. The discovery and targeting of oncogene driven subsets of NSCLC including EGFR-mutant NSCLC, which comprises about 15% of NSCLC has revolutionized treatment of lung cancer. NSCLC tumors with EGFR-activating mutations are exquisitely sensitive to EGFR tyrosine kinase inhibitors (EGFR-TKIs) with overall response rates (ORR) of approximately 60-70%. However, resistance to currently approved EGFR-TKIs (afatinib, gefitinib, erlotinib) invariably develop with a median PFS of approximately 9-11 months. Broad mechanisms of resistance include target alterations such as EGFR T790M (~50-60%), which is the most common mechanism of acquired resistance to EGFR-TKIs and prevents the TKI from fastening to the ATP binding domain of EGFR, bypass tract generation such as PIK3CA mutations, MET amplification and Her2 amplification (~20%) as well as target amplification of EGFR (~10%)[2, 3].

2.2 CTEP IND AGENTS

2.2.1 OSI-774 (Erlotinib)

Background

OSI-774 (erlotinib, Tarceva®) is an orally active, potent, selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase [4]. OSI-774 inhibits the human EGFR tyrosine kinase with a 50% inhibitory concentration (IC_{50}) of 2 nM (0.786 ng/mL) in an *in vitro* enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.86 ng/mL). OSI-774 inhibits EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell-cycle progression in the G_1 phase.

OSI-774 appears to bind specifically to EGFR. In a study of OSI-774 binding specificity, affinity of OSI-774 for 67 cellular receptors was examined [4]. OSI-774 was shown to bind with low affinity to peripheral benzodiazepine (IC_{50}=2.5 μM [980 ng/ml]), adenosine A_1 (IC_{50}=6.8 μM [2700 ng/ml]), and μ-opiate (IC_{50}=7.0 μM [2800 ng/ml]) receptors. Binding affinities were

1250-fold higher than the IC_{50} concentration needed to inhibit purified EGFR tyrosine kinase (2 nM [0.79 ng/ml]). When tested at concentrations up to 1 μM (390 ng/ml), no significant inhibition of ligand binding to 64 other neurotransmitter receptors, regulatory binding sites, calcium channels, opioid receptors, or neurotransmitter uptake sites were observed.

Nonclinical Studies

In mice, daily oral administration of OSI-774 for 20 days inhibited subcutaneous (SC) growth of the HN5 human head and neck carcinoma in a dose-dependent manner as compared to vehicle-treated mice, with an estimated effective dose for 50% inhibition (ED_{50}) of 9.2 mg/kg/day [4]. Treatment with 11 mg/kg/day of OSI-774 immediately halted growth or slightly decreased the size of HN5 tumors >1 cm in diameter. The tumor stasis profile appeared to extend beyond the treatment period such that the tumor size for OSI-774-treated animals did not exceed pretreatment levels until at least 33 days post-treatment. Similar results were observed in A431 squamous cell carcinoma xenografts at a dose of 11 mg/kg/day OSI-774 over 20 days.

OSI-774 (10 mg/kg/day) has been studied in combination with cisplatin, doxorubicin, 5-fluorouracil, paclitaxel, vinorelbine tartrate, and gemcitabine [4]. No antagonism of therapeutic efficacy was observed, and additive effects were observed with cisplatin (10 mg/kg intravenous [IV] daily × 1), doxorubicin (15 mg/kg IV daily × 1), paclitaxel (10 mg/kg intraperitoneal [IP] daily × 5), and gemcitabine (100 mg/kg IP three times daily × 4).

Nonclinical toxicology studies in rats and dogs have included acute and long-term general toxicology, genetic toxicology, reproductive toxicology, and local tissue tolerance of OSI-774. Clinical signs of toxicity in rats and/or dogs following a single dose of OSI-774 were dose dependent and included transient emesis, ataxia, papillary dilation, increased heart rate, decreased blood pressure, decreased activity, irregular respiration, convulsions, rapid chewing, salivation, and death. Following chronic administration in rats and dogs, the following toxicities were observed in at least one species: effects on the cornea (atrophy and ulceration); effects on the skin (follicular degeneration and inflammation, redness, and alopecia); atrophy of the ovary, lacrimal glands, and salivary glands; necrosis of the liver; papillary necrosis and tubular dilatation of the kidney; inflammation in the mandibular lymph nodes; hematopoiesis; delayed gastric emptying; and diarrhea. Increases in alanine aminotransferase, aspartate aminotransferase, and bilirubin were observed.

OSI-774 causes maternal toxicity with associated embryo-fetal lethality and abortion in rabbits at doses 3 times those in humans (AUC at 150 mg daily dose). However, when administered during organogenesis at plasma concentrations approximately equal to humans, no increase in embryo-fetal lethality or abortion in rats or rabbits was observed. Female rats treated with doses 0.3 to 0.7 times the human dose prior to mating and during the first week of gestation had an increase in early resorptions. No teratogenic effects were observed in rats or rabbits.

Pharmacokinetics

The total clearance of OSI-774 decreased with increasing dose, resulting in supraproportional increases in exposure (AUC) over the dose range of 1-2 mg/kg IV in rats and 0.5-7 mg/kg IV in

dogs [4]. *In vitro*, OSI-774 is slowly oxidized by liver microsomes. The majority of the absorbed dose is extensively metabolized in rats and dogs, and only a small amount is excreted as unchanged drug in urine, bile, and feces. The oral bioavailability of an aqueous suspension is 77% in rats and ~88% in dogs. Plasma protein binding of OSI-774 ranges from 92% to 95% in man, monkey, rat, and mouse, and is 85% in the dog. Corrected for protein binding of 95%, at the average plasma concentration responsible for 50% inhibition of tumor growth (oral dose of 9.2 mg/kg/day in the murine/human tumor xenograft model), the unbound concentration of drug in the plasma is estimated to be 86 nM (34 ng/mL). The estimated unbound concentration of OSI-774 in plasma is consistent (4-fold higher) with the IC_{50} for the *in vitro* cellular phosphotyrosine reduction assay and is 43-fold higher than the IC_{50} for the *in vitro* (isolated enzyme) tyrosine kinase assay. Finally, OSI-774 plasma protein binding depends on the levels of α-1-acid glycoprotein (AAG). Thus, AAG might be a significant determinant of pharmacokinetic and possibly pharmacokinetic–pharmacodynamic relationships in patients.

Pharmacokinetic Data

OSI-774 pharmacokinetics were examined in patients with advanced solid tumors who were treated daily for 21 days. Plasma samples were collected on Days 1, 3, and 21 for analysis. The following table lists the pharmacokinetic data for these patients:

Mean (%CV) OSI-774 Pharmacokinetic Parameters following Daily Dosing

Dose (mg)	N	AUC_{0-24} (ng•h/ml)			R*		C_{avg} (ng/ml)			C_{max} (ng/ml)		
		Day 1	Day 3	Day 21	Day 3	Day 21	Day 1	Day 3	Day 21	Day 1	Day 3	Day 21
25	3	1580 (40)	2180 (49)		1.38 (11)		66	91		208 (38)	310 (40)	
50	6[a]	5650 (54)	5790 (57)	14900 (69)	1.59 (31)	1.83 (30)	235	241	621	508 (34)	716 (55)	682 (59)
100	8[b]	9210 (92)	9080 (49)	32200 (148)	1.75 (35)	3.21 (56)	384	378	1340	765 (69)	1140 (49)	1740 (85)
150	7[c]	14200 (71)	20600 (22)	45800 (99)	1.74 (6.7	2.57 (47)	670	859	1910	1040 (70)	2040 (21)	1730 (82)
200	7	36000 (34)		74200 (29)		2.01 (42)	1360		3200	1420 (47)		2910 (29)

Abbreviations: AUC_{0-24}, Area under the time-concentration curve from 0 to 24 hours; C_{avg}, daily average plasma concentration; C_{max}, maximum serum/plasma concentration; CV, coefficient of variance; R, accumulation ratio

*Accumulation ratio = $AUC_{Day\ 3\ or\ 21}/AUC_{Day\ 1}$

[a]Only 3 patients day 3, 3 subjects day 21

[b]Only 2 patients day 3, 3 subjects day 21

[c]Only 6 patients day 21

After oral ingestion, the OSI-774 C_{max} values (T_{max}) were achieved at a median of 3 hours (range, 2 to 12 hours). Both C_{max} and AUC_{0-24} values were roughly proportional to the OSI-774 dose in the range of 25 to 200 mg/d (R2 = 0.33 and 0.46, respectively, on Day 1). Inter-subject variability was moderate at the 150-mg/d dose level, as indicated by coefficient of variation values of 64% for Day 1 AUC_{0-24} and C_{max}.

Dose Rationale

Dosing of erlotinib will be at the FDA approved dose of 150 mg daily.

2.2.2 ONALESPIB (Onalespib lactate)

Background

Onalespib (AT13387) is a synthetic non-ansamycin small molecule that acts as an inhibitor of heat shock protein 90 (HSP90). HSP90 inhibitors are thought to affect multiple aberrant signaling pathways and may therefore be of clinical benefit in the treatment of a wide range of cancers.

Nonclinical Studies

Onalespib potently inhibits HSP90 in human tumor cell lines and demonstrates antitumor activity against human tumor cell line xenografts in mice. In vivo studies suggest that onalespib leads to a prolonged inhibition of HSP90 in tumors. In cancer xenograft models in mice (NSCLC driven by mutated EGFR or translocated ALK; vemurafenib-sensitive and -resistant melanoma), onalespib inhibited tumor growth and was best tolerated weekly or twice weekly. In upfront combination with kinase inhibitors, onalespib was able to delay the emergence of resistance in melanoma and NSCLC xenograft models.

The onset of onalespib toxicity was characterized by adverse clinical signs, reduced food consumption, hematologic and clinical chemistry effects. Data were obtained in an acute pilot study (clinical observations and necropsy), DRF studies (clinical observations and clinical pathology and necropsy), and definitive studies (full toxicologic investigations). Results from these studies provide a clear picture of the safety and toxicity of onalespib given by a 1-hour infusion.

The toxicity profile of onalespib was similar in rats and dogs. Both species exhibited decreased body weight and food consumption, and decreases in white blood counts, as well as clinical pathology changes. The overall effects observed in surviving rats and dogs were transient and reversible, with the exception of the testicular lesions observed in dogs at high doses which had not reversed during 14 days recovery.

TK data showed good characterization of onalespib concentration-time profiles achieved for 1 hour IV infusion and plasma concentration-time profiles were consistent with this mode of administration. Exposure was confirmed in all test article dosed groups on Study Days sampled

and increased an approximately dose-related manner. No onalespib was detected in any control vehicle-dosed animal samples. There were no consistent gender differences. There was no significant accumulation or decrease in exposure upon repeat IV administration. Onalespib was essentially completely cleared from plasma by 24 hours.

In rats, onalespib was administered over 1 hour, either through the tail vein or a femoral vein cannula, as a single dose or repeated. Both methods of administration were problematic in rats, as tail vein administration led to severe toxicity and femoral vein administration led to thrombus formation. In the definitive rat study, a surgically implanted femoral vein cannula was associated with thrombus formation and occasional early deaths, as confirmed by histopathologic investigations.

The main results from these studies were as follows:
• Clinical pathology changes suggestive of adverse effects in various organs including bone marrow, kidney and liver were observed at doses ≥50 mg/kg, but histopathology was not examined
• No unambiguous target organs of toxicity were identified, and the NOAEL was estimated to be 50 mg/kg/dose given twice weekly for 3 weeks
• Consequently a dose severely toxic to 10% of rodents (STD10) could not be confidently determined in rats although safety was established in this species
In dogs, a clear dose-effect relationship was established for onalespib (administration through a peripheral vein). Dogs were more sensitive than rats on a dose basis (mg/kg and mg/m2) and an exposure basis (Cmax and AUC). Histopathology in dogs revealed changes in the bone marrow, thymus, testes, gall bladder, and kidney at 3, 10/7, and 12.5/10/7 mg/kg. The nominal HNSTD was 3 mg/kg/dose given twice weekly for 3 weeks. The NOAEL was taken to be 1mg/kg/dose on the same schedule.

A subsequent repeat-dose study of two new onalespib formulations to assess potential acute toxicity and local infusion site irritation in rabbits revealed that higher pH (less acidic) phosphate-buffered formulation caused less infusion-site irritation. However, exposures in rabbits at the 25 mg/kg dose were more than 2-fold higher than in humans (at the MTD dose of 260 mg/m2) and as a consequence, the repeat-dose regimen was not tolerated in rabbits, as mortalities occurred in all groups. Due to adverse findings secondary to cannulation in rats, as well as no detection of unambiguous target organs of toxicity in rats, an STD10 could not be confidently determined in the rat. A clear dose-related toxicity was established in dogs, including identification of target organs of toxicity; the NOAEL was 1 mg/kg/dose given 2QW×3 and the nominal HNSTD was 3 mg/kg/dose given 2QW×3. The dog was found to be more sensitive than the rat on a mg/kg and mg/m2 basis, as well as in exposure terms (Cmax and AUC). The human clinical start dose was calculated on a mg/m2 basis using accepted body surface area conversion factors (FDA 2005). Given its high sensitivity to onalespib, the dog was deemed an appropriate species for this purpose; therefore, the start dose was estimated as one-sixth of the nominal dog HNSTD (HNSTD = 3 mg/kg = 60 mg/m2), giving a human start dose of 10 mg/m2/dose given 2QW×3. The human start dose calculated from the dog HNSTD is 3-fold lower than would be derived from the rat NOAEL (start dose based on one tenth of the rat NOAEL on a body surface area basis = 30 mg/m2/dose).

Pharmacokinetics

• After intravenous (IV) administration to mice, rats, and dogs and intraperitoneal (IP) administration to mice, onalespib displayed a short plasma half-life in mice and rats (1-3 hours) and a moderate half-life in dogs (11 hours) despite high plasma clearance. Volume of distribution was greater than total body water indicating distribution of onalespib into tissues. PK studies demonstrated that onalespib is highly distributed into xenograft tumors and is cleared slowly from tumors.

• The in vitro intrinsic clearance of onalespib determined in isolated intact hepatocytes was high across all the species tested (mouse, rat, dog and human; scaled values ranged from 35 mL/min/kg in human to 184 mL/min/kg in rat).

• Binding of onalespib to plasma proteins was moderate and comparable across all species tested, ranging from 77.2% in dog plasma to 90.1% in mouse plasma.

• Blood:plasma distribution in mouse, rat, dog and human whole blood ranged from 0.8, indicating approximately equal distribution between the plasma and cellular fraction, to 5.0, showing that onalespib favored partitioning into the red blood cells, depending on concentration and species.

• The potential for onalespib to inhibit cytochromes P450 (CYP) 1A2, 3A4, 2D6, 2C9, and 2C19 was assessed, and results indicated a concentration giving half-maximal inhibition (IC50) >10μM, suggesting a low potential for clinically significant drug-drug interactions mediated by these enzymes.

• Onalespib is a substrate for P-gp, a modest inhibitor of BCRP and P-gp, and strong inhibitor of MATE1 and MATE2-K.

• Glucuronidation, sulphation and N-oxidation appear to be routes of metabolism for onalespib based on in vitro studies of cryopreserved hepatocytes as well as metabolites detected in samples in vivo.

• In a radiolabeled mass balance study in dogs, a mean maximum measured concentration (Cmax) of 793 ng-Eq/g occurred at the end of infusion. Area under the curve concentration-time curve from time 0 to the last data point (AUC0-t) values were 5924 hr•ng-Eq/g and 7590 hr•ng-Eq/g for male and female dogs, respectively, with halflife (t1/2) values of 21.3 and 20.5 hour, respectively. The majority (~83% in the male and ~72% in the female) of [14C]onalespib-derived radioactivity was excreted via feces, with less found in urine (~15% in the male and ~22% in the female).

• The PK of onalespib showed dose-dependent increase in AUC0-t and Cmax from 10 to 310 mg/m2/dose with relatively low inter-individual variability. Elimination half-life (t1/2 el) was dose-independent with mean cohort values ranging from 6.6 to 11.5 hours. Maximum t1/2 observed was 14 hours. There was no notable accumulation or reduction in exposures between Day 1 and Day 18 (twice weekly) or Day 1 and Day 15 (once weekly) of Cycle 1.

• The onalespib PK profile and exposures were similar across several studies, whether as a single agent (ONALESPIB-01) or in combination with imatinib (ONALESPIB-02), abiraterone acetate (ONALESPIB-04), or crizotinib (ONALESPIB-05), at comparable dose levels, indicating no potential for interactions affecting onalespib PK by these agents.

• Plasma increases in HSP70 were detected at all dose levels in Study ONALESPIB-01. HSP70 induction is a pharmacodynamic marker of target engagement, but has not been demonstrated to be predictive of clinical response.

Clinical Studies

• ONALESPIB-01, Phase 1 study in adults with metastatic solid tumors who receive onalespib monotherapy.

• ONALESPIB-02, Phase 2 study in adults with gastrointestinal stromal tumor (GIST) who receive onalespib in combination with imatinib. Disease control at 4 months occurred in 5 (19.2%) subjects.

• ONALESPIB-03 (CTEP 8828), Phase 1 study sponsored by the National Cancer Institute (NCI) in adults with refractory solid tumors who receive onalespib monotherapy.

• ONALESPIB-04, 2-part, Phase 1-2 open-label, parallel-group, randomized study in subjects with castration resistant prostate cancer (CRPC) who are no longer responding to treatment with abiraterone acetate and steroids.

• ONALESPIB-05, 3-part Phase 1-2 study in subjects with ALK+ or other potentially crizotinib-sensitive NSCLC. 4 PRs have been reported during the dose-escalation part of the study (Part A).

• ONALESPIB-EP-01 (CTEP 9557), Phase 1 study sponsored by the National Cancer Institute (NCI) in adults with BRAF-inhibitor resistant patients with BRAF-mutant melanoma who receive onalespib in combination with dabrafenib and trametinib.

• In Study ONALESPIB-01 (monotherapy), the best response to treatment was 1 partial response (PR) in a subject with GIST and stable disease persisting for ≥6 months in 4 subjects (2 with GIST, 1 with adenoid cystic carcinoma of the right parotid, 1 with metastatic uveal melanoma).

Clinical Toxicities

Limited information on the metabolism, elimination, and safety of onalespib is currently available. Onalespib appears to be metabolized by the liver and both parent compound and metabolites eliminated by the kidneys.

Until further information is available, subjects with the following organ impairment or abnormalities should be excluded (according to the specific criteria defined in the clinical study protocol):

• Clinically significant abnormal liver function as demonstrated by serum bilirubin >1.5 times the upper limit of normal (ULN) or ALT or AST >2.5 times the ULN (or >5 times the ULN in the presence of liver metastases).
• Impaired renal function as demonstrated by serum creatinine >1.25 ULN or creatinine clearance <50 mL/min.
• Left ventricular ejection fraction <50% on echocardiography or multigated acquisition (ECHO/MUGA) scan.

QTc >450 ms, or as specified in the individual clinical study protocol. Any clinically significant electrolyte imbalance, particularly hypokalemia and hypomagnesemia, should be corrected before treatment. Cumulative safety data from the ongoing trials may result in relaxing some of the above recommendations in later-stage clinical studies.

The most common SAEs by System Organ Class (SOC; subjects counted once per SOC), regardless of relationship, through the cut-off date of 30 December 2014, were categorized under Respiratory, Thoracic, and Mediastinal Disorders (23/237; 10%); Gastrointestinal Disorders (17/237; 7%); and General Disorders and Administration Site Conditions (12/237; 5%). Individual event terms reported for >3 subjects were 8/237 (3.4%) for dyspnea (6 resolved, 1 decreased in severity, and 1 not resolved); 6/237 (2.5%) for diarrhea (5 resolved and 1 not resolved); 5/237 (2.1%) each for dehydration (4 resolved and 1 resolved with sequelae) and pulmonary embolism (4 resolved and 1 not resolved); and 4/237 (1.7%) each for back pain (all resolved), muscular weakness (1 resolved, 1 decreased in severity, and 2 not resolved), and pneumonia (2 resolved and 2 fatal).

Dose Rationale

Dedicated drug-drug interaction studies have not been conducted. However, The potential for onalespib to inhibit cytochromes P450 (CYP) 1A2, 3A4, 2D6, 2C9, and 2C19 was assessed, and results indicated a concentration giving half-maximal inhibition (IC50) >10μM, suggesting a low potential for clinically significant drug-drug interactions mediated by these enzymes. Olanespib PK does not appear to be affected when coadministered with imatinib (ONALESPIB-02), abiraterone acetate (ONALESPIB-04), or crizotinib (ONALESPIB-05). PK studies of ONALESPIB and assessment of drug-drug interactions with erlotinib will be conducted in this study. Erlotinib is primarily metabolized by CYP3A4 and CYP3A5 in liver and intestine, and to a lesser extent, by CYP1A2 and CYP2C8. While caution is recommended when erlotinib is co-administered with either strong inducers or inhibitors of CYP3A4/5, there is no evidence that onalespib will impact the metabolic clearance of erlotinib.

This phase 1 trial dose escalates onalespib to the recommended Phase 2 dose (RP2D) to a maximum of 220 mg/m2 once weekly, which is the MTD and/or RP2D for other combination studies of onalespib (combination with imatinib, crizotinib in ALK rearranged NSCLC, or abiraterone acetate+ steroid).

2.3 Rationale for Trial

EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib have revolutionized treatment of advanced NSCLC patients whose tumors harbor EGFR activating mutations (EGFR+). Unfortunately, on average 30-40% of these patients do not respond to EGFR inhibitors and resistance invariably develops with a median PFS of 9-10 months[5, 6]. Mechanisms of resistance to erlotinib include: EGFR T790M mutations (~50%), MET, EGFR and Her2 amplification (~30%), EMT and small cell transformation (~10%) and acquired PIK3CA mutations (~10%)[2, 3].

There is an unmet clinical need for new active therapies for patients that circumvent resistance to EGFR-TKIs and improve clinical outcomes in EGFR-mutant NSCLC.

Current approaches to address this unmet need include second generation EGFR-TKIs such as afatinib (recently approved in the first line setting for treatment of metastatic EGFR-mutant NSCLC[7]) though it has not been directly shown to be superior to 1st generation EGFR-TKIs such as erlotinib or gefitinib in the first line setting and single agent response rates to afatinib in patients who have progressed on 1st generation EGFR-TKIs are low (~7%).[8] Third generation EGFR-TKIs such as AZD9291 and CO-1686 have shown promise in patients who have progressed on 1st generation EGFR-TKIs with high response rates (50-60%) in patients whose tumors harbor the EGFR-T790M resistance mutation, though they are mainly specific for EGFR-T790M with less selectivity and much lower response rates in patients with EGFR-mutant NSCLC lacking EGFR-T790M[9, 10].

Hsp90 is a molecular chaperone that participates in stabilizing and activating hundreds of client proteins. In cancer cells, Hsp90 preferentially protects mutated and overexpressed oncoproteins from misfolding and degradation[11]. The Hsp90 inhibitor onalespib potently inhibits Hsp90 chaperone activity and promotes degradation of numerous client proteins including many oncoproteins that mediate resistance to erlotinib. Maintaining prolonged knockdown of Hsp90 client proteins with Hsp90 inhibitors has been a challenge in the development of this class of drugs in NSCLC[12]. Oncoprotein knockdown by onalespib is prolonged in NSCLC cell lines and xenotransplants, offering a potential advantage of onalespib over other Hsp90 inhibitors in development[13]. onalespib has single agent activity and is synergistic with erlotinib in EGFR+ NSCLC cell lines and xenotransplants[14, 15]. Since Hsp90 inhibitors preferentially degrade several overexpressed oncoproteins known to mediate resistance to erlotinib (including EGFR T790M, Her2, PIK3CA, MET) and multiple mechanisms of EGFR-TKI resistance can exist within the same tumor[16], we hypothesize that onalespib added to erlotinib can circumvent or delay EGFR-TKI resistance in a broad population of EGFR-mutant NSCLC and target multiple mechanisms of EGFR-TKI resistance that may exist within the same patient[16].

Cell Line	EGFR Genotype	Erlotinib Sensitivity	AT13387 IC_{50} (nM)	Erlotinib IC_{50} (nM)
HCC827	Del E746_A750	sensitive	33	57
NCI-H1975	L858R/T790M	resistant	30	>10 000
NCI-H1650	Del E746_A750 PTEN del	Intermediate/ resistant	54	>10 000
NCI-H820	Del E746_L751/ T790M/Met↑	resistant	49	>10 000
HCC827R	N/D (generated in-house)	resistant	24	> 10 000

HCC827R cell line was generated by culturing HCC827 cells in the presence of increasing concentrations of erlotinib until resistance was acquired.

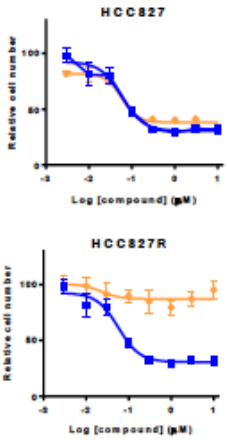


Figure 1: EGFR-mutant NSCLC is sensitive to Hsp90 inhibition with onalespib including erlotinib resistant cell lines (from Wallis, N. et al. WCLC 2014).

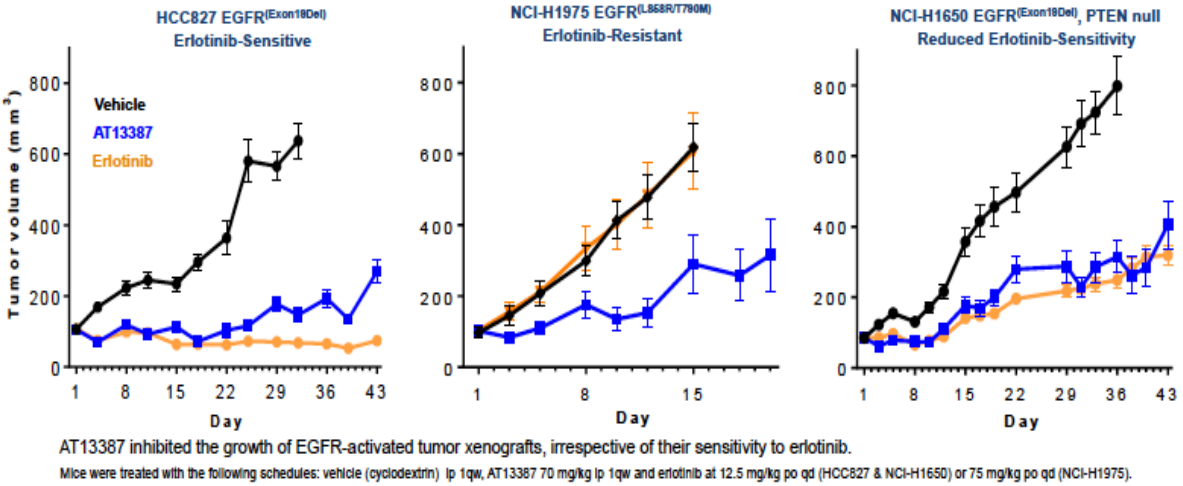


Figure 2: Onalespib inhibits growth of EGFR-mutant tumor xenografts irrespective of sensitivity to erlotinib (from Wallis, N. et al. WCLC 2014).

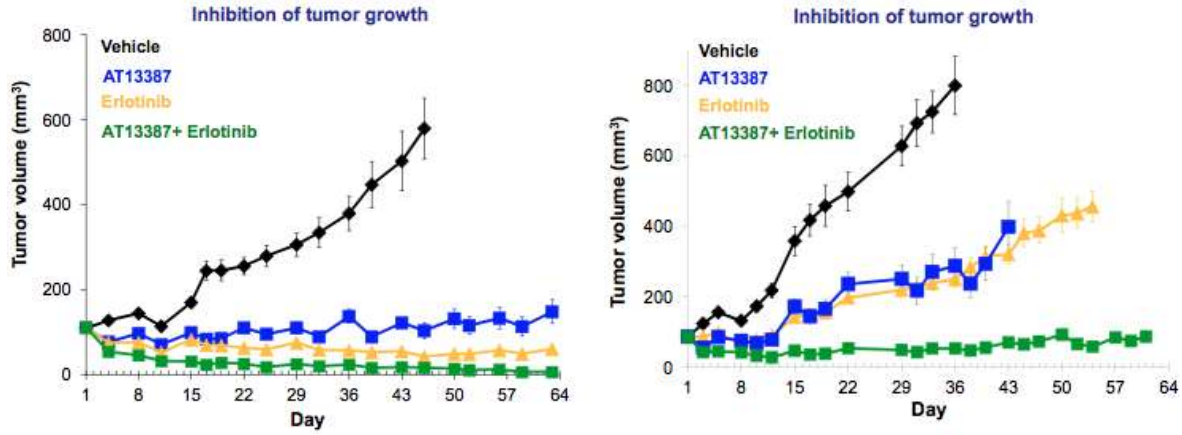


Figure 3: Combination onalespib and Erlotinib inhibits growth of EGFR-mutant tumor xerografts irrespective of sensitivity to erlotinib (HCC827 – EGFR E19del Left, NCI-H1650 - EGFR E19del and PTEN del right) (From Smyth, T. et al. AACR 2014).

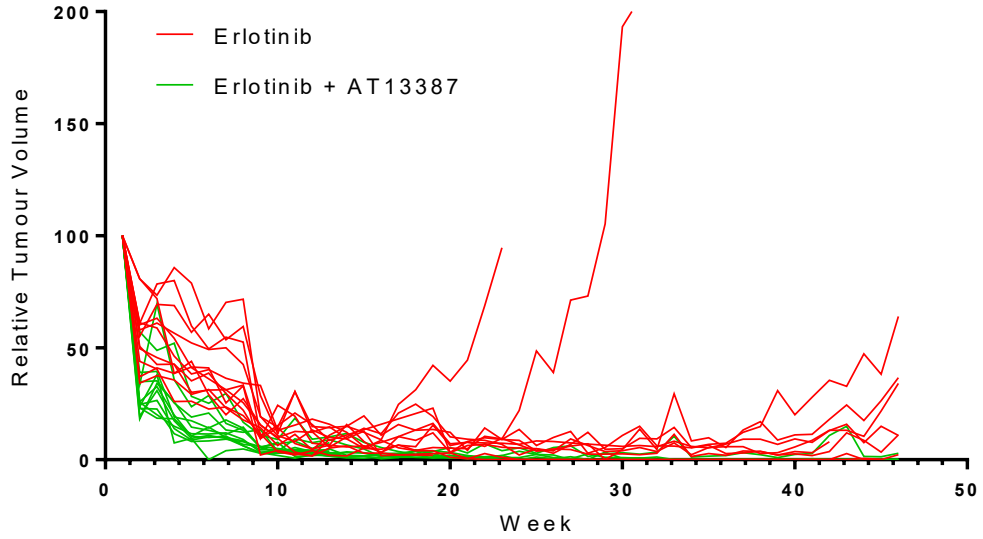


Figure 4: Combination erlotinib and onalespib delays resistance in an EGFR-mutant xenograft model (HCC827). Only the erlotinib alone treated xenografts had relapsed disease (confidential from Astex – Presented at AACR 2015).

Compared to the two classic EGFR mutations (EGFR Exon 19 deletions and EGFR L858R) EGFR exon 20 insertions are less common EGFR mutations that are not typically responsive to EGFR-TKIs with reported response rates <10%[17]. Hsp90 inhibitors have pre-clinical activity in EGFR Exon 20 insertions with cell line evidence showing Exon 20 insertions with interaction and dependence on Hsp90[18]. Generating in vivo models of exon 20 insertions as we proposed with the creation of patient derived xenografts is critical to developing new treatments for this uncommon EGFR-mutation. Clinical activity of Hsp90 inhibition has been recently described with the Hsp90 inhibitor AUY922 in NSCLC patients with EGFR-Exon 20 Insertions (Z. Piotrowska et al, ASCO 2015). However, night blindness and other toxicities may inhibit further development of this HSP90 inhibitor. This trial combines onalespib with erlotinib in a dedicated phase 2 study because select EGFR Exon 20 insertions may be sensitive to EGFR-TKIs, albeit with a low single agent EGFR-TKI response rate (RR 5-10%)[17].

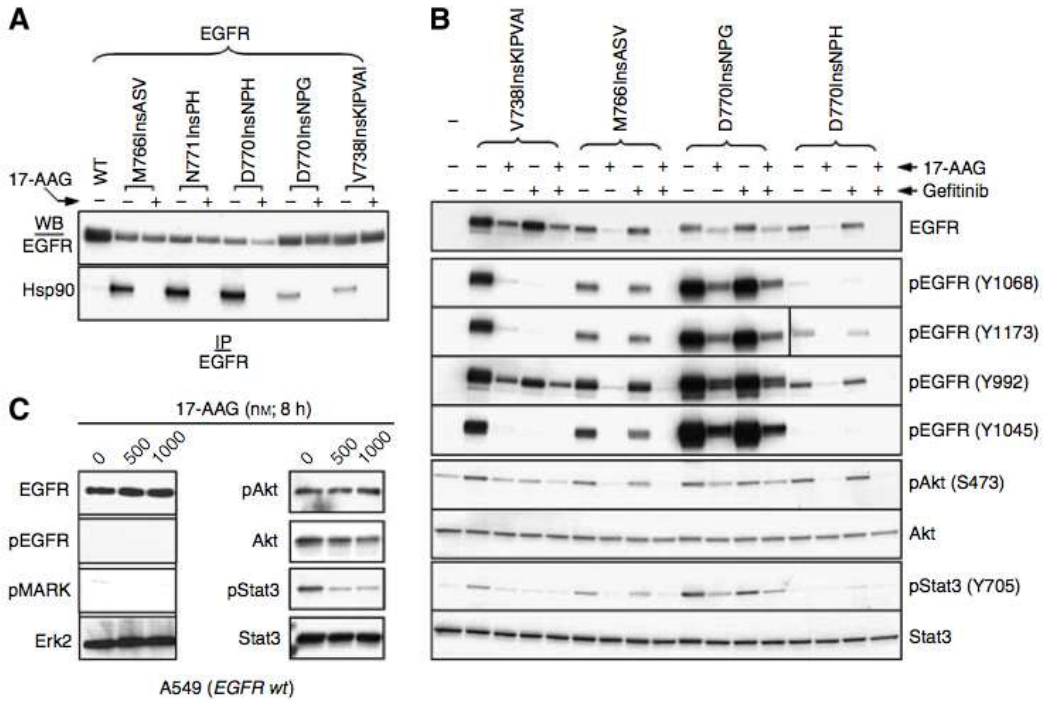


Figure 5: Exon 20 insertion mutations in EGFR confer interaction with and dependence on Hsp90. (**A**) Epidermal growth factor receptor exon 20 insertion mutants display 17-AAG-sensitive association with Hsp90. COS7 cells were transfected with wild type or mutant EGFR constructs as described in Materials and Methods. One day after transfection, cells were treated with/without 0.5μm 17-AAG for 1h, and Hsp90 association with EGFR was monitored by coimmunoprecipitation analysis. Membranes were probed sequentially for Hsp90 and EGFR as shown. (**B**) Stability, autophosphorylation, and downstream signaling of EGFR exon 20 insertion mutants are inhibited by 17-AAG. Two days after transfection, COS7 cells were treated with 0.5μm 17-AAG, 0.1μm gefitinib, or a combination of the two drugs for 5h. Cells were lysed and processed as described in Materials and Methods. Individual membranes were probed as indicated. The EGFR phosphorylation sites examined form docking sites linking the activated receptor to various downstream effectors: EGFR/pY1068 associates with Grb2, Stat3/5, and Gab1; EGFR/pY1173 associates with Shp1 and Ptp1; EGFR/pY992 associates with PLCγ and Shc; and EGFR/pY1045 associates with Cbl. (**C**) A549 cells, expressing wild-type EGFR, were treated with 17-AAG as shown. Cells were lysed and processed as described in Materials and Methods, and Western blots were probed as in (**B**) above. (From Xu et al, British Journal of Cancer 2007).

In the more classic EGFR-activating mutations, based on the promising preclinical data and mechanism of action of onalespib, we propose a phase 1/2 trial of erlotinib and onalespib to determine safety and tolerability and then assess preliminary efficacy by seeing if we can induce responses with the combination in patients with EGFR-activating mutations who have not responded to frontline single-agent erlotinib.

2.4 Correlative Studies Background

EGFR-mutation Testing (Integrated Biomarker)

This trial will accept EGFR-mutation testing by any CLIA-certified laboratory for patient enrollment and treatment as EGFR-mutation testing is standard of care. Response Genetics is a CLIA certified laboratory that will perform EGFR-mutation testing by Sanger Sequencing as central confirmation of EGFR-mutation status and determination of EGFR-T790M. Response Genetics is also the vendor for EGFR-mutation testing for the adjuvant erlotinib ALCHEMIST study in NSCLC sponsored by NCI.

Plasma cfDNA (Guardant 360) (Integrated Biomarker)

Description of the Assay

Guardant360 is a cell-free circulating tumor DNA (ctDNA) targeted next-generation sequencing (NGS) panel that is indicated for the prevention of a repeat invasive biopsy when the initial biopsy is QNS or unavailable/unobtainable as well as when cancer has progressed or recurred despite treatment. It is an advanced diagnostic laboratory test (ADLT) offered by a sole source Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathology (CAP)-accredited laboratory. This solid tumor profiling panel sequences 68 clinically actionable genes for single nucleotide variants and copy number variations in 16 genes with a simple blood test [1]. The genes are selected because mutations in these genes have FDA-approved matched therapies or are eligible for late phase clinical trials. The panel also includes genomic markers of acquired resistance that may require a change in pharmacotherapy.

Advantages of the Guardant360 cell-free DNA (cfDNA) NGS methodology versus solid tumor tissue-based NGS are:

1. An invasive needle or surgical biopsy is avoided with cfDNA, reducing costs and complications.
2. CfDNA provides a *quantitative* measure (concentration or mutant allele frequency) of mutations present whereas solid tumor biopsy typically provides a qualitative result (mutation either present or not detected). The quantitative result may be followed over time to monitor response to treatment and evolution of acquired resistance.
3. CfDNA sequencing identifies *both* germline and somatic mutations.
4. The assay failure rate is for cfDNA is essentially null (0.5% in the first 2,000+ samples) compared to 15%-25% failure rates of tissue-based NGS related to insufficient quantity of tissue (QNS).

The key differentiator of the Guardant360 cfDNA NGS panel compared to other ctDNA panels is that the latter are limited to hotspot or "hot exon" analysis due to the high false positive rates related to longer sequencing regions at the low concentrations encountered with ctDNA. The high rates of false positives with current NGS assays when tumor DNA is in very low concentrations has limited the majority of methods for circulating tumor DNA (ctDNA) to hotspot analyses, amplicon sequencing approaches and/or typically involve patients where the ctDNA fraction is greater than 1-5% of total circulating cfDNA. To overcome these limitations, Guardant360 utilizes algorithmic methods to encode and ultimately decode inputs and outputs from massively parallel deep sequencing analysis. By leveraging signal transduction processing technology where voice or image data is digitally encoded before transmission and then decoded post-transmission, this NGS method, known as Digital SequencingTM, enables signal interference to be reduced by two orders of magnitude or more [2]. With high enough sensitivity and specificity to robustly quantitate ctDNA from blood, this approach has the potential to evaluate the multiple genomic targets required in NCCN guidelines, to act as a "summary" of the different tumor clones in patients with intra-tumor and inter-tumor heterogeneity [3], and to prevent the time delays, costs and complications inherent in invasive biopsies. The analytical and clinical validation of Guardant360 is conducted in conformance with evidentiary standards established by the Standards for Reporting of Diagnostic Accuracy (STARD), REporting of

tumor MARKer Studies (REMARK), Evaluation of Genomic Applications in Practice and Prevention (EGAPP), and the recent Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) biomarker guidelines **[4–7]**.

Methodology

The Guardant360 ctDNA next generation sequencing assay identifies single nucleotide variants (SNVs) in 68 genes and includes complete exon coverage of 29 genes and coverage of partial exons ("hot exons") in 39 genes, including copy number variants in 16 genes (see figure at end of this report).

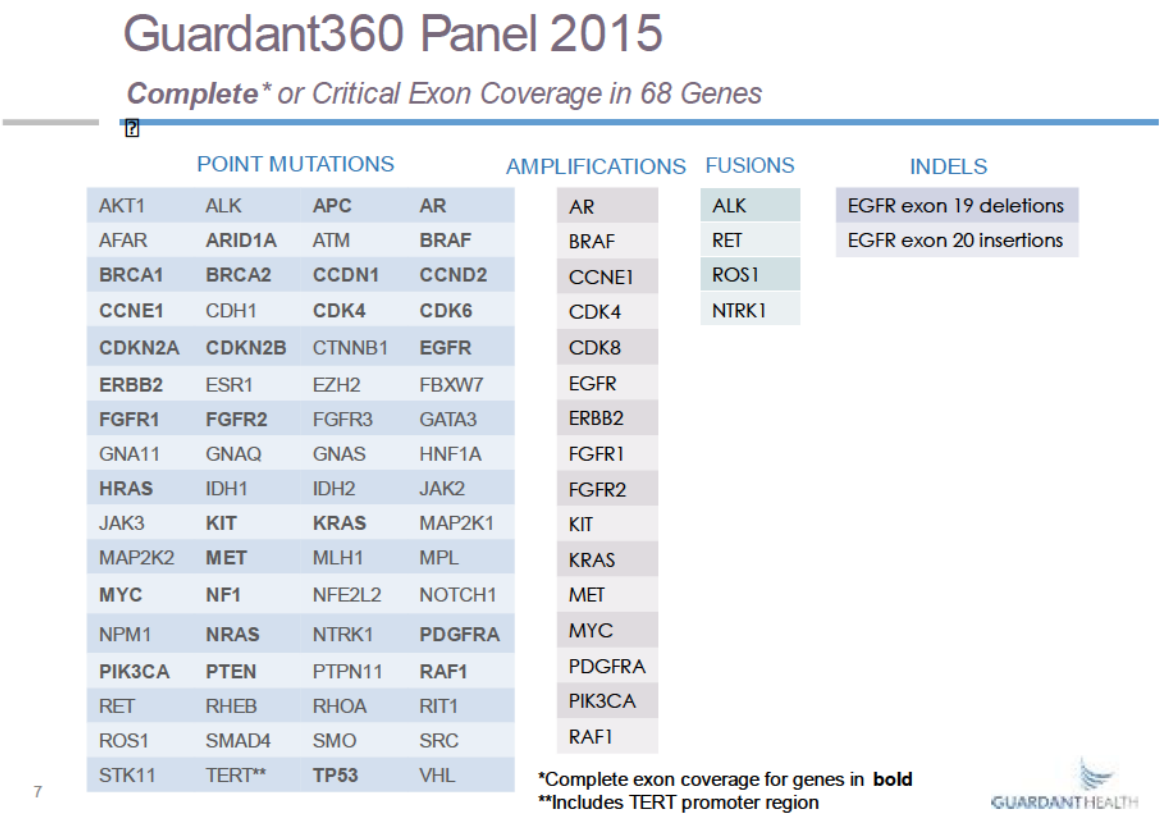
The gene list was selected to focus on those genomic alterations that are currently actionable defined as being targets of sensitivity or resistance to an FDA-approved matched therapy and/or a targeted therapy in clinical trials. The test simultaneously sequences the 68 cancer-related genes to an average depth of coverage of greater than 10,000X. To summarize, cell-free DNA is extracted from plasma and genomic alterations are analyzed by massively parallel paired end synthesis-by-sequencing of amplified target genes utilizing an Illumina Hi-Seq 2500 platform complemented by systematic end-to-end process optimization including conversion of cell-free DNA fragments into digital sequences, improvements in the Illumina next generation sequencing process itself, followed by bioinformatics algorithms which enable ctDNA to be measured as a quantitative percentage of total cell-free DNA.

Two 10mls of whole blood are collected in Streck Cell-Free DNA Blood Collection (Streck) tubes, which contain a proprietary formaldehyde-free preservative in that stabilizes white blood cells, preventing the release of genomic DNA and allowing shipping and stability for seven days without need for refrigeration, cold bricks or preliminary centrifugation prior to shipping.

After digital libraries are produced, the sample is sequenced and post-sequencing data is processed using bioinformatics algorithms to quantify the absolute number of unique DNA fragments at a given nucleotide position. This proprietary process is referred to as Digital Sequencing™ and enables reporting of the fractional concentration (mutant allele frequency) of a given SNV. Circulating cell-free DNA is mostly derived from leukocyte lysis (germline) and generally a much smaller amount of tumor DNA is derived from cancer cell apoptosis/necrosis. All of the cell-free DNA fragments, including leukocyte-derived and tumor-derived, are simultaneously sequenced with up to single molecule sensitivity. In other words, both tumor DNA and "normal"/germline DNA are sequenced and measured in the same sequencing assay. The fractional concentration or mutant allele frequency for a given mutation is calculated as the fraction of circulating tumor DNA harboring that mutation in a background of wild-type cell-free DNA fragments. The analytic sensitivity reaches detection of 1-2 single mutant fragments from a 10 ml blood sample.

Leveraging the ability of Digital Sequencing™ to absolutely quantify the number of unique DNA fragments in a sequenced sample, the copy number of a given gene in plasma may be ascertained. To determine the copy number variant (CNV) or amplification of a given gene, we first measure the total number of unique fragments covering each gene. The mode of the normalized number of fragments covering each gene is calculated to estimate the fragment

number corresponding to 2 copies to derive a baseline diploid value. All values of unique fragments for each gene are then normalized by this baseline value. The same procedure is employed using a large set of normal samples from healthy donors (Normal Set). The normalized concentration of a given gene in the sample is compared to its concentration in the Normal Set. The numerical result of the above procedure expresses the absolute copy number of a gene in plasma-derived cfDNA samples, which is a combination of both normal cell-free DNA (mainly leukocyte-derived) and tumor-derived gene copy number. Because most of the cell-free DNA is typically germline-derived, a small elevation in the gene copy number in plasma may reflect a much higher copy number in the tumor. For example, if the *ERBB2* (HER2 protein) gene copy number in the tumor was 10.0, and 5% of the DNA in cell-free DNA was tumor-derived and 95% was leukocyte-derived (germline copy number 2.0), then the *ERBB2* copy number in plasma would be 2.3.



The Guardant 360 gene panel incorporates the main resistance mechanisms to EGFR-TKIs (EGFR CNG, MET CNG, EGFR T790M, PIK3CA, BRAF, HER2 amplification). We plan to use the Guardant assay to detect mechanisms of resistance to EGFR-TKI and explore correlations with clinical outcomes. We also plan to use presence/absence of EGFR Exon 20 insertions on cfDNA as an exploratory marker of clinical benefit in Cohort B of the phase 2 study. Presence or absence of EGFR-mut has been demonstrated to be a prognostic marker in EGFR-mutant NSCLC in the FASTACT-2 trial of intercalated EGFR-inhibitor and chemotherapy[1, 19].

The Guardant 360 assay is already incorporated into other NCI sponsored clinical trials such as the SWOG study of Afatinib and Cetuximab as frontline treatment of EGFR-mutant NSCLC, in pancreatobiliary cancer and in clinical trials of the 3rd generation EGFR-TKI rocilitinib where it is used to select for EGFR-TKI (OA Zill, Cancer Discovery 2015).

Pharmacokinetics (Integrated biomarker)

There are no expected interactions between onalespib and erlotinib. As this combination has not been explored before we will send a subset of samples for pharmacokinetic analysis conducted by a third party bioanalytical laboratory selected by Astex.

Multiplex Immunofluorescence Assay (MIFA) of Hsp90 Target Genes (Exploratory Biomarker)

Maintaining prolonged knockdown of Hsp90 client proteins with Hsp90 inhibitors has been a challenge in the development of this class of drugs [9]. A critical component of successful drug development of Hsp90 inhibitors is demonstrating pharmacodynamic (PD) knockdown of client oncoproteins related to erlotinib resistance in patients. A major obstacle to lung cancer research is the paucity of diagnostic tissue available for biomarker analysis – often limited to a single core needle biopsy. Our approach minimizes usage of precious clinical specimens by analyzing multiple markers on a single slide and detects co-expression of key resistance factors in a single tumor cell. In contrast to traditional fluorescent imaging, bright-field conversion allows assessment by trained pathologists concurrent with quantitative measurements of expression.

This technique will be used to simultaneously assess tumor expression of EGFR exon 19 del, EGFR L858R, EGFR wild-type, MET and HER2 in biopsied specimens using a Nuance 2 Multispectral Imaging System Model (Perkin Elmer) attached to an Olympus fluorescent microscope and inForm advanced image analysis software.

The Mack laboratory at UC Davis has extensive experience in the MIFA assay including incorporation into NCI sponsored studies such as SWOG 0931 Everest study of the mTOR inhibitor everolimus as adjuvant therapy in Renal Cell Carcinoma and FGF/FGFR.

We are currently optimizing the assay to deploy in this clinical trial with optional biopsies at baseline and on treatment shortly after receiving onalespib. Demonstrating in vivo on-target activity of Hsp90 inhibition in this disease will help elucidate the mechanisms underlying potential clinical benefit of the treatment combination; demonstrate proof-of-principle for prolonged Hsp90 client oncoprotein knockdown in patients with EGFR-mutant NSCLC treated with erlotinib and onalespib and aid in the identification of subsets of patients with EGFR-mutant NSCLC who may preferentially benefit from this combination.

Using MIFA, we hypothesize that we can detect changes in Hsp90, Hsp70 and client oncoproteins that may mediate resistance to EGFR-TKI (MET, Her2, EGFR overexpression) in pre-treatment and on-treatment biopsies with erlotinib and onalespib.

Oncopanel (Next Generation Sequencing) (Exploratory Biomarker)

EGFR-tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib have revolutionized treatment of advanced NSCLC patients whose tumors harbor EGFR activating mutations (EGFR+). Unfortunately, resistance to EGFR-TKIs invariably develops, with a median PFS of 9-11 months[5, 6]. Acquired EGFR T790M mutations that prevent the EGFR-TKI from fastening to the ATP-binding domain via steric hindrance is the most common mechanism of resistance (~50-60%). Other mechanisms of resistance include: BRAF mutations, NF1 loss, MET, EGFR and Her2 amplification (~30%), EMT, small cell transformation (~10%) and acquired PIK3CA mutations (~10%)[2, 3]. Mechanisms of resistance to erlotinib in combination with Hsp90 inhibition are unknown. In addition to the most common EGFR-TKI resistance mechanism (EGFR T790M), we plan an exploratory analysis via next generation sequencing to comprehensively explore mechanisms of resistance prior to initiation of onalespib and erlotinib and at progression on this trial to further define mechanisms of resistance to the combination.

Patient Derived Xenografts (PDXs) (Exploratory Biomarker)

Patient-derived xenografts (PDXs) recapitulate the molecular, histological and treatment response profile of the original patient tumor. This enables the efficacy of modified or alternative therapies to be tested in a controlled, laboratory setting to identify regimens with enhanced activity and ability to overcome patient-specific resistance mechanisms emergent in the study population. Co-investigators at The Jackson Laboratory and UC Davis Comprehensive Cancer Center have a wealth of experience in establishing, maintaining and testing PDX models derived from NSCLC[20].

We plan to establish patient-derived xenografts from fresh tumor samples collected at the time initiation and acquired resistance to study therapy.

Establishment of cell cultures and/or patient-derived xenografts from fresh samples collected at resistance (Jackson Laboratory). Tumor material will be used to establish PDX models from patients enrolled on this study including those with EGFR Exon 20 insertions a subset of EGFR-mutant NSCLC where PDX models do not exist. At select institutions, fresh tumor specimens from biopsies before initiation of treatment with erlotinib and onalespib and at time of progression on this treatment will be viably shipped overnight to the JAX-West facilities in Sacramento for implantation as per the established protocol.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Phase 1: Patients must have metastatic/recurrent, histologically confirmed NSCLC that harbors an EGFR activating mutation (Exon 21 L858R, Exon 19 deletion, Exon 18 G719X, Exon 21 L861Q) with progressive disease by RECIST 1.1 on a previous EGFR-TKI.

OR

Patients must have metastatic/recurrent histologically confirmed NSCLC that harbors an EGFR Exon 20 insertion with progressive disease on platinum containing chemotherapy.

3.1.2 Phase 2 Cohort A:

Patients must have metastatic/recurrent histologically confirmed NSCLC that harbors an EGFR activating mutation (Exon 21 L858R, Exon 19 deletion, Exon 18 G719X, Exon 21 L861Q) with stable disease by RECIST 1.1 as best response on erlotinib compared to pre-treatment erlotinib imaging by RECIST 1.1 or progressive disease compared to pre-treatment imaging by RECIST 1.1 after a minimum duration of treatment on erlotinib of 12-weeks. Patients must be enrolled within 6 months of initiation of erlotinib.

3.1.3 Phase 2 Cohort B:

Patients must have metastatic/recurrent histologically confirmed NSCLC that harbors an EGFR Exon 20 insertion with progressive disease on or after platinum doublet chemotherapy.

3.1.4

- For phase 1: if patient is on erlotinib at the time of signed consent, the patient does NOT need to be discontinued prior to initiation of erlotinib and onalespib. Other EGFR-TKIs must be discontinued at least 7 days prior to initiation of erlotinib and onalespib.

- For Phase 2 Cohort A: If patient is on erlotinib at the time of signed consent, erlotinib does NOT need to be discontinued prior to receiving treatment erlotinib and onalespib. Last dose of erlotinib must be less than 28 days from when patient signs consent.

- For Phase 2 Cohort B: (EGFR Exon 20 Insertions): Prior EGFR-TKIs including erlotinib is allowed. If patient is on erlotinib at the time of signed consent, erlotinib does NOT need to be discontinued prior to initiation of erlotinib and onalespib.

3.1.5 Local testing for EGFR-mutations for this study is acceptable provided it was performed in a CLIA certified lab.

3.1.6 Patients with a prior history of brain metastases are eligible provided:

a. The brain metastases have been treated
b. The patient is asymptomatic from the brain metastases
c. Corticosteroids prescribed for the management of brain metastases have been discontinued at least 7 days prior to registration

3.1.7 Patients must have completed last chemotherapy ≥ 3 weeks or radiotherapy ≥ 2 weeks prior to receiving study drugs.

3.1.8 Patients must have recovered from adverse events attributable to previous treatment to ≤ grade 1, except for alopecia and sensory neuropathy ≤ grade 2.

3.1.9 Measurable disease by RECIST 1.1

3.1.9.1 Age ≥18 years. Lung cancer is exceedingly rare in children. Because no dosing or adverse event data are currently available on the use onalespib in combination with erlotinib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

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

3.1.11 Life expectancy of greater than 3 months.

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 x UNL of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- PT/INR and PTT	< 1.3 ULN

3.1.13 The effects of erlotinib and onalespib on the developing human fetus are unknown. For this reason and because onalespib and erlotinib may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of erlotinib and/or onalespib administration.

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

3.2 Exclusion Criteria

3.2.1 Patients who are receiving any other investigational agents.

3.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib and/or onalespib

3.2.3 History of pneumonitis attributed to an EGFR inhibitor. History of radiation pneumonitis is allowed provided steroid administration for pneumonitis was not required.

3.2.4 Mean resting corrected QT interval (QTc using Fredericia's formula (QTcF)) > 470 msec (See Appendix E for Fridericia's formula).

3.2.5 Left ventricular ejection fraction ≤ 50% as demonstrated by echocardiogram or MUGA.

3.2.6 Drugs that are known to increase torsades de pointes should be avoided. Patients must discontinue these medications prior to enrollment on study. Please see Appendix D for current list of drugs to avoid. Selection of alternate concomitant medications with no or minimal torsades de pointes potential is recommended. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as medical reference texts with crediblemeds.org as an example.

3.2.7 Strong CYP3A4 inducers and inhibitors should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

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

3.2.9 Pregnant women are excluded from this study because erlotinib and onalespib has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with erlotinib and onalespib, breastfeeding should be discontinued if the mother is treated with erlotinib and onalespib.

3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with erlotinib and/or onalespib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.11 Prior treatment with a Hsp90 inhibitor.

3.2.12 Treatment with proton pump inhibitors within 3 days prior to study entry.

- If treatment with an H2-receptor antagonist such as ranitidine is required, Erlotinib must be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist.
- Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and the erlotinib dose should be separated by several hours, if an antacid is necessary.

3.2.13 Abnormalities of the cornea based on history (e.g., dry eye syndrome, Sjogren's syndrome), congenital abnormality (e.g., Fuch's dystrophy), abnormal slit-lamp examination using a vital dye (e.g., fluorescein, Bengal Rose), and/or an abnormal corneal sensitivity test (Schirmer test or similar tear production test).

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff

requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

- Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following: An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9878 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-CA043, and protocol #9878.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 9878 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' section) → Regulatory Tab → Regulatory Submission Portal

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

• Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).
• City of Hope Cancer Center will receive notification via the IWRS when a slot has been reserved. An email will be sent from the City of Hope Cancer Center to the site requesting further information such as: the patient initials, tumor type and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION FORM/ELIGIBILITY CHECKLIST accompanied with the signed consent, baseline labs, pathology report, CT/x-ray reports to the City of Hope Cancer Center at ccc@coh.org for review and confirmation of eligibility.
• Once the Registration has been reviewed, the City of Hope Cancer Center will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the City of Hope Cancer Centre will update the spot to 'reserved' in IWRS.
• The site can now enroll the patient into the study in OPEN.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL (*Note: A DTL is NOT required for this study)*.

- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.
This trial has two stages. Stage 1 (Phase 1) is dose escalation using a 3+3 design and stage 2 (phase 2) will be opened at MTD dose. See Section 13.1 for further details.

Dose Level	Erlotinib (Oral, Daily)	Onalespib (IV, weekly D1, D8, D15)
-1	150 mg	120 mg/m2

0 (Starting)	150 mg	150 mg/m2
+1	150 mg	180 mg/m2
+2	150 mg	220 mg/m2

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Onalespib	*Premedicate with dexamethasone and/ or antihistamine ONLY if previous infusion reaction occurs.*	*** in 250 cc D5W or normal saline*	*IV over 1 hour,* ***after*** *erlotinib*	*Days 1, 8, 15.*	*28 days (4 weeks)*
Erlotinib		*150 mg tablet*	*PO in the a.m. 1 hour before or 2 hours after a meal.*	*Daily*	
***Doses as appropriate for assigned dose level.*					

The patient will be requested to maintain a medication diary of erlotinib (Appendix C). The medication diary will be returned to clinic staff at the end of each course.

Erlotinib Administration

- Tablets should be taken once daily preferably in the morning with up to 200 mL of water 1 hour before or 2 hours after food.
- If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.
- Patients should log in their daily dose onto a "Pill Diary," including missed, skipped, or vomited doses.
- Patients should wear sunscreen protection, hat, and long sleeves to avoid sun as it can exacerbate skin rash.

- On the day of the PK studies, i.e., C1D8, erlotinib is to be administered 30 minutes before the administration of Onalespib IV. Please see Section 9.1.3 for additional information.

5.2 Definition of Dose-Limiting Toxicity

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 5.0. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

- ≥ Grade 3 non-hematologic toxicity
- Except nausea, vomiting or diarrhea that can be controlled by appropriate medical intervention or prophylaxis and that resolves to ≤ grade 1 within 48 hours with medical intervention
- Except electrolyte toxicities that can be corrected to ≤ grade 1 or baseline within 48 hours
- Grade 3 rash attributed to the combination will be considered a DLT if grade 3 despite maximal medical management (including oral antibiotic, topical or oral steroids) for > 72 hours
- Febrile neutropenia; grade 4 neutropenia for >7 days
- Thrombocytopenia <25,000/mm^3 (grade 4) if associated with:
  - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
  - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
  - Grade 5 toxicity (i.e., death)
- Pneumonitis ≥ grade 3
- Delay in starting cycle 2 of ≥ 14 days due to toxicity related to one or more protocol drugs
- Infusion related reactions such as hypersensitivity reaction from onalespib will not be assessed as a DLT regardless of grade.

Dose intensity in cycles beyond cycle 1 will be considered in the assessment of the recommended phase 2 dose. To be evaluable for a DLT, 75% of dose must have been administered in cycle 1 unless a DLT occurred.

Management and dose modifications associated with the above adverse events are outlined in Section 5 and Section 6.

5.3 Dose Escalation Guidelines

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. Patients will be considered to have received an informative course of therapy for the purpose of dose escalation rules if: (a) after any amount of study drug, the patient suffers a DLT, or the course is curtailed to prevent an impending DLT; or (b) the patient receives all three planned infusions of Onalespib and at least 75% of the planned dose of erlotinib. The patient will be considered fully followed for their initial course if either a DLT is reported, or the adverse event form indicates that reporting is complete for the course. Patients who have not received an informative and fully followed first course of therapy will be replaced to obtain the necessary denominator for the dose-escalation rules.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of erlotinib and onalespib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The

potential targets for drug interaction can involve, but are not limited to CYP450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton-pump inhibitors. Drugs that are known to increase torsades de pointes should be avoided. Check the study agent Investigator's Brochure for potential sources of drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

Erlotinib

Rash: In some patients, rash appeared to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, or oral prednisone (short course).

Diarrhea: Previous trials have shown that the frequency and severity of diarrhea rarely hindered administration of Erlotinib (OSI-774) and could be managed with loperamide. The recommended dose is loperamide 4 mg at first onset, followed by 2 mg every 2–4 hours until diarrhea-free for 12 hours.

Drugs affecting gastric pH

- Avoid concomitant use of Erlotinib (OSI-774) with proton pump inhibitors if possible. Separation of doses may not eliminate the interaction since proton pump inhibitors affect the pH of the upper gastrointestinal (GI) tract for an extended period.
- If treatment with an H2-receptor antagonist such as ranitidine is required, Erlotinib (OSI-774) must be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist.
- Although the effect of antacids on Erlotinib (OSI-774) pharmacokinetics has not been evaluated, the antacid dose and the Erlotinib (OSI-774) dose should be separated by several hours, if an antacid is necessary.

Onalespib Infusion Reaction

Local infusion-related irritation and systemic infusion reactions may occur during or shortly after the administration of onalespib. The local infusion adverse events are formulation-related (pH of current formulation is ~ 4.0). Systemic adverse events (e.g.; flushing, itching, rigors, chills, nausea, tachycardia/bradycardia, dizziness) are reversible. If that occurs, slow the infusion rate and/or hydrate with D5W. Premedication with dexamethasone, antihistamine and 5HT3 antagonists can also be given.

5.5 Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.6 Duration of Follow Up

Patients will be followed every 12 weeks for one year and then annually after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose modification criteria

If an adverse event that qualifies as a DLT (including those that occur beyond Cycle 1) is observed in any subject, the dose should be withheld until there is sufficient recovery that satisfies the study eligibility criteria in terms of organ function. Dosing may be resumed in that subject, after recovery, but at a reduced dose 1 level below the dose at which the DLT occurred. If the toxicity recurs, another dose level reduction should be performed or treatment discontinued. A subject's dose may be reduced for a ≥ Grade 2 toxicity, if the Investigator deems it necessary.

Interstitial Lung Disease (Pneumonitis)

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is determined to be related to study drugs**,** study drugs must be permanently discontinued and appropriate treatment instituted as necessary.

Dose Modifications for Erlotinib

All dose levels for erlotinib are at the FDA approved starting dose of erlotinib 150 mg PO daily.

Table 1. Erlotinib (OSI-774) Dose Level Reductions

Starting Dose	Dose (-1)	Dose (-2)
150 mg/day	100 mg/day	50 mg/day

After dose -2 (50 mg/day) of erlotinib, no further dose reduction levels are permitted. The patient must then discontinue erlotinib. If the investigator determines the patient is deriving clinical benefit from onalespib, onalespib may be continued as a single agent at the investigators discretion.

Dose Modification and Management of Adverse Events Consistent with Erlotinib Use

Toxicity	**Grade**	**Erlotinib (OSI-774) dosage modification***	**Guideline for management**
Keratitis	1	None	No intervention
	2 (if ≤14 days)	None	Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks
	2 (if >14 days)	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level	
	≥3	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level*	
	≥3	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level	
Bilirubin	(for patients without pre-existing liver dysfunction) >3 x ULN	Withhold OSI-774. Discontinue if levels do not improve significantly or resolve within three weeks.	
	(for patients with pre-existing liver dysfunction) ≥2 x baseline		

Toxicity	Grade	Erlotinib (OSI-774) dosage modification*	Guideline for management
Liver trans-aminase	(for patients without pre-existing liver dysfunction) ≥5 x ULN	Withhold OSI-774. Discontinue if levels do not improve significantly or resolve within three weeks.	
	(for patients with pre-existing liver dysfunction) ≥3 x baseline		
Signs and symptoms of interstitial pneumonitis		Hold pending diagnosis Permanently discontinue if diagnosis is confirmed and considered possibly related to Erlotinbi (OSI-774	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated
Other toxicity	≥2 prolonged clinically significant toxicity	Hold until recovery to ≤ grade 1 And then Reduce 1 dose level*	Treatment as appropriate
*if dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level			

Discontinue Erlotinib (OSI-774) for:

- Severe hepatic toxicity that does not improve significantly or resolve within three weeks.
- Gastrointestinal perforation.
- Severe bullous, blistering or exfoliating skin conditions.
- Corneal perforation or severe ulceration.

Withhold Erlotinib (OSI-774):

- For severe (grade 3 to 4) renal toxicity, and consider discontinuation of OSI-774.
- For acute/worsening ocular disorders such as eye pain, and consider discontinuation of OSI-774.

Reduce Erlotinib (OSI-774) by 50 mg decrements:

- When restarting therapy following withholding treatment for a dose-limiting toxicity that has resolved to baseline or grade ≤1.

Dose Modifications for Onalespib

The dose levels for this study are as follows:

• Starting dose: 150 mg/m^2 weekly for 3 weeks in a 4-week cycle,

• Escalation to dose levels of 180 mg/m^2 then to 220 mg/m^2 weekly for 3 weeks in a 4-week cycle, and

• Dose reduction to 120 mg/m^2 weekly for 3 weeks in a 4-week cycle.

If dose reduction of onalespib is required or deemed necessary by the investigator, onalespib should be reduced to the doses outlined in the following table.

onalespib **IV** **(Day 1, Day 8, Day 15)**	**Reduce Dose of** onalespib **IV** **(Day 1, Day 8, Day 15)**
220 mg/m^2	180 mg/m^2
180 mg/m^2	150 mg/m^2
150 mg/m^2	120 mg/m^2

No further dose reduction levels are permitted beyond 120 mg/m^2. The patient must then discontinue onalespib. If the investigator determines the patient is deriving clinical benefit from erlotinib, erlotinib may be continued as a single agent at the investigators discretion.

Specific dose reduction schemes for erlotinib and onalespib for diarrhea and skin toxicity are outlined below.

Diarrhea Management on Erlotinib and Onalespib

Patients should be instructed to use loperamide for the prevention of diarrhea and initiate upon the first loose stool (4 mg at first onset, followed by 2mg every 2-4 hours until diarrhea resolves for 12 hours). Patients should notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management. Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson, Ajani et al. 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. The dose modification guidance the tables below should be followed. In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Dose Modification and Management of Diarrhea

Toxicity, NCI-CTCAE Grade	**Action To Be Taken With Erlotinib**	**Action To Be Taken With Onalespib**	**Recommended Guidelines For Management**
Diarrhea			
Grade 1	No change in dosage	No change in dosage	Administration of antidiarrheal agents is recommended at the first sign of diarrhea. Loperamide is recommended as standard first line therapy Alternatively, diphenoxylate can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include tincture of opium and octreotide (Benson et al. 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate, and tincture of opium for optimal management of diarrhea.
Grade 2	No change in dosage. Reduce dose of erlotinib if necessary (at investigators discretion) if diarrhea persists over 72 hours despite optimal medical management	No change in dosage. Reduce dose of onalespib if diarrhea persists over 72 hours despite optimal medical management **after** erlotinib dose has been reduced.	
Grade 3 (despite optimal management)	Hold erlotinib. Restart erlotinib at reduced dose when diarrhea resolves to Grade ≤ 1.	Hold onalespib initially. Restart onalespib with no dose change when diarrhea resolves to Grade ≤ 1. Reduce dose of onalespib if Grade 3 diarrhea recurs despite optimal medical management after erlotinib dose has been reduced.	
Grade 4	Discontinue erlotinib	Hold onalespib initially. Restart onalespib at a reduced dose when diarrhea resolves to Grade ≤ 1. Discontinue onalespib if Grade 4 diarrhea recurs despite optimal medical management.	

Dose Modification and Management of Rash Consistent with Erlotinib Use

Toxicity, NCI-CTCAE Grade	**Action To Be Taken With Erlotinib**	**Action To Be Taken With Onalespib**	**Recommended Guidelines For Management**
Rash Consistent with the Use of Erlotinib			
Grade 1	No change in dosage.	No change in dosage	Any of the following: minocycline or doxycycline, topical tetracycline, topical clindamycin, topical hydrocortisone, topical pimecrolimus, topical silver sulfadiazine, or diphenhydramine at discretion of investigator
Grade 2	No change in dosage. Reduce dose of erlotinib if necessary if rash persists or worsens over 10-14 days despite optimal medical management	No change in dosage.	Manage as described above
Grade 3	Hold erlotinib. Restart erlotinib at reduced dose when rash is Grade ≤ 2.	Hold onalespib initially. Restart onalespib with no dose change when rash resolves to Grade ≤ 2. . Reduce dose of onalespib if Grade 3 rash recurs (or if rash does not resolve to Grade ≤ 2 within 2 weeks) after erlotinib dose has been reduced.	Manage as described above

Grade 4	Discontinue erlotinib	Hold onalespib initially. Restart onalespib with no dose change when rash resolves to Grade ≤ 2. Discontinue onalespib if Grade 4 rash recurs.	Manage as described above

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for OSI-774 (Erlotinib, NSC 718781)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3622 patients.* Below is the CAEPR for OSI-774 (erlotinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, June 20, 2017[1]

Adverse Events with Possible Relationship to Erlotinib (Tarceva) (CTCAE 4.0 Term) [n= 3622]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Disseminated intravascular coagulation[2]	
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Myocardial infarction[2]	
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
	Dry eye		***Dry eye (Gr 2)***
		Eye disorders - Other (corneal perforation)	
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***

Adverse Events with Possible Relationship to Erlotinib (Tarceva) (CTCAE 4.0 Term) [n= 3622]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Gastrointestinal hemorrhage[3]		
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 3)***
		INR increased (in patients taking Coumadin)	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular[2]	
RENAL AND URINARY DISORDERS			

Adverse Events with Possible Relationship to Erlotinib (Tarceva) (CTCAE 4.0 Term) [n= 3622]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
	Pneumonitis		***Pneumonitis (Gr 4)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Nail loss		***Nail loss (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The risk of myocardial infarction, cerebrovascular accident, and microangiopathic hemolytic anemia is increased in patients with pancreatic cancer who were treated concomitantly with gemcitabine.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on erlotinib (Tarceva) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that erlotinib (Tarceva) caused the adverse event:

EYE DISORDERS - Blurred vision; Eye disorders - Other (orbital cellulitis); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Duodenal ulcer; Dysphagia; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (pneumatosis intestinalis); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs
HEPATOBILIARY DISORDERS - Cholecystitis
INVESTIGATIONS - Creatinine increased; Lymphocyte count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Dizziness; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pharyngolaryngeal pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria
VASCULAR DISORDERS - Thromboembolic event

Note: Erlotinib (Tarceva) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: Erlotinib (Tarceva®)-induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

Note: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of erlotinib (Tarceva®) in patients with or without baseline hepatic impairment.

7.1.1.2 CAEPR for Onalespib (AT13387) (NSC 749712)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 119 patients.* Below is the CAEPR for AT13387 (Onalespib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.0, April 6, 2017[1]

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 4.0 Term) [n= 119]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
EYE DISORDERS			
	Blurred vision		
	Eye disorders - Other (visual impairment)		***Eye disorders - Other (visual impairment) (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Flatulence		***Flatulence (Gr 2)***
	Gastrointestinal hemorrhage[2]		
	Hemorrhoids		***Hemorrhoids (Gr 2)***

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 4.0 Term) [n= 119]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		***Fever[3] (Gr 2)***
	Infusion related reaction[3]		***Infusion related reaction[3] (Gr 2)***
Injection site reaction[4]			***Injection site reaction[4] (Gr 2)***
	Malaise		***Malaise (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased		***CPK increased (Gr 2)***
	Electrocardiogram QT corrected interval prolonged		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 4.0 Term) [n= 119]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		***Hyponatremia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		***Musculoskeletal and connective tissue disorder - Other (muscle spasms) (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Hiccups		***Hiccups (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Hyperhidrosis[3]		***Hyperhidrosis[3] (Gr 2)***
	Rash acneiform		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic

hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infusion-related reactions may include, tachycardia/bradycardia, hypotension/hypertension, flushing, chills, fever, hyperhidrosis, itching, rigors, and abdominal cramps.

[4]Injection site reaction may include injection site irritation, injection site pain, injection site inflammation or redness, or erythema.

[5]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on AT13387 (Onalespib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AT13387 (Onalespib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Cardiac disorders - Other (atrioventricular block NOS); Left ventricular systolic dysfunction; Palpitations
EYE DISORDERS - Dry eye; Eye disorders - Other (color distortion); Eye disorders - Other (diplopia); Eye disorders - Other (halos); Eye disorders - Other (loss of visual acuity during changes in ambient light levels); Eye disorders - Other (tunnel vision); Eye disorders - Other (visual color darkening); Eye disorders - Other (visual disturbances); Eye pain; Flashing lights; Floaters; Keratitis; Night blindness; Papilledema; Photophobia; Retinopathy
GASTROINTESTINAL DISORDERS - Colitis; Mucositis oral; Oral dysesthesia; Oral pain; Salivary duct inflammation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills[3]; Flu like symptoms
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Creatinine increased; Ejection fraction decreased; Neutrophil count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypoalbuminemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Pruritus; Skin hyperpigmentation
VASCULAR DISORDERS - Hypertension[3]

Note: AT13387 (Onalespib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may

result in events never previously associated with either agent.

Note: Onalespib dose should be based on the most current weight available and recalculated based on weight and BSA at least at the beginning of each cycle and for a threshold change in weight of > 10%.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent(s)

8.1.1 Erlotinib (OSI-774) (NSC 718781)

Chemical Name: N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride

Other Names: Erlotinib hydrochloride, Tarceva™

Classification: Tyrosine kinase Inhibitor (EGFR)

Molecular Formula: $C_{22}H_{23}N_3O_4 \cdot HCl$ **M.W.**: 393.4 (free base) 429.9 (hydrochloride salt)

Mode of Action: Direct inhibition of EGFR tyrosine kinase

How Supplied: Erlotinib tablets are provided by Astellas Pharma and distributed by the Pharmaceutical Management Branch, DCTD/NCI as 25 mg, 100 mg, and 150 mg white film-coated immediate-release tablets packaged in high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets.

The tablets are round and convex without markings. The 25 mg tablets are 1/4 inches (6 mm); the 100 mg tablets are 11/32 inches (9 mm); and the 150 mg tablets are 13/32 inches (10 mm). Erlotinib excipients include lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow No. 6 (25 mg only) for product identification.

In 2017 there will be a transition to Erlotinib tablets with a different finished appearance. The new Erlotinib tablets are manufactured to the same specifications, and are packaged in 60 mL HDPE bottles. The tablets are round, with a biconvex face, straight sides, and white film-coated. Each strength will be plain on one side, with print on the opposite side:

- 25 mg – "T" and "25" in orange print
- 100 mg – "T" and "100" in gray print
- 150 mg – "T" and "150" in maroon print

Storage: Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F).

Route of Administration: Oral.

Method of Administration:

- Tablets should be taken once daily preferably in the morning with up to 200 mL of water one hour before or two hours after food.

- Administration through G-tube: Dissolve the dose in 100 mL of sterile water, and shake it vigorously to form a uniform suspension. Draw suspension into a syringe and administer through the G-tube port. Repeat the transfer until the entire volume has been administered. Add small volume (40 mL) of sterile water to the container used to dissolve the tablets. Shake the residual suspension, aspirate it into a syringe, and administer. Repeat this last step to ensure the entire dose is administered. The total volume of delivery/rinse is ~180 mL.

Potential Drug Interaction: Erlotinib is highly protein bound (92% to 95% in humans). Erlotinib is metabolized primarily via CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Dose Erlotinib cautiously with agents that are highly protein bound or are metabolized by, or are inhibitors or inducers of these enzymes.

Significant interactions with the clearance of other CYP3A4 substrates are unlikely.

CYP Iso-Enzymes Inhibitors/Inducers:

- Potent CYP3A4 or combined CYP3A4/CYP1A2 Inhibitors: Use alternative drug. Alternatively, reduce Erlotinib dose in the event of drug interaction (if permitted by the protocol).
- Potent CYP3A4 inducers: Use alternative drug. If an alternative treatment is contraindicated, consider increasing the Erlotinib dose (if permitted by the protocol).
- Potent and moderate CYP1A2 inducers: concomitant use with Erlotinib should be avoided.

Food-drug interaction: Avoid grapefruit /grapefruit juice (potent CYP3A4) while taking Erlotinib.

Smoking: Advise smokers to stop smoking while Erlotinib. Smoking induces CYP1A2 enzymes and has been shown to reduce Erlotinib exposure by 50% to 60%.

Anticoagulant: Concomitant NSAIDs, warfarin or warfarin-derivatives may increase bleeding and PT /INR. Dose adjustment may be needed.

Proton Pump Inhibitor: Erlotinib's solubility decreases as the pH increases. Co-administration of omeprazole with Erlotinib will increase the AUC and C_{max} by 46% and 61%, respectively.

H_2-antagonist: Avoid concomitant use of Erlotinib with gastric acid reducing agents if possible. When ranitidine 300 mg is given with Erlotinib, Erlotinib AUC and C_{max} decrease by 33% and 54%, respectively. Increasing the dose of Erlotinib will not compensate the loss of exposure. However, if an H_2-antagonist receptor is needed, **take Erlotinib at least 2 hours before or 10 hours following the H_2-antagonist administration.** Dosing such, Erlotinib loss of exposure is minimized to AUC of 15% and C_{max} of 17%.

Statins: The combination of erlotinib and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Patient Care Implications: If patient vomits after taking the tablets, readminister the dose only if the tablets can actually be seen and counted.

Recommend patients to use sunscreen protection, and wear hat and long sleeve shirts as sunlight can exacerbate skin reactions.

Women of childbearing potential must use effective contraception during treatment and for one month after the last dose of Erlotinib.

Availability

Erlotinib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Erlotinib is provided to the NCI under a Clinical Trials Agreement (CTA) between Astellas Pharma and the DCTD, NCI.

SAFETY PROFILE

Adverse Events (AEs) Associated with Erlotinib

A comprehensive list of AEs possibly related to Erlotinib is provided in the CAEPR. Additional information can also be found in the Investigator's Brochure. A few common or serious AEs are described below.

Interstitial lung disease (ILD): Cases of ILD-like events, including fatalities, have been reported uncommonly in patients receiving OSI-774 for treatment of non-small cell lung cancer (NSCLC), pancreatic cancer, or other advanced solid tumors. In pivotal study BR 21, in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and OSI-774 arms. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the OSI-774 plus gemcitabine group versus 0.4% in the placebo plus gemcitabine-treated group. The overall incidence in patients treated with OSI-774 from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events include pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute

respiratory distress syndrome, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating OSI-774 therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections. In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever, OSI-774 therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, OSI-774 should be discontinued and appropriate treatment initiated as necessary.

Rash or dermatosis: Rash or dermatosis (grades 1-3) has been reported in many subjects (~50%) during the first several days of treatment, although severity diminishes after 4 weeks of therapy. The use of topical agents (*i.e*., diphenhydramine, corticosteroids) and oral antibiotics (tetracycline) has been instituted in some patients with variable results. In patients with severe rash, treatment has been discontinued or the study drug dose reduced. The etiology of the rash is still unknown, but may be related to the mechanism of action of OSI-774.

Diarrhea, dehydration, and electrolyte imbalance: Diarrhea has occurred in patients on OSI-774, and moderate or severe diarrhea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, OSI-774 therapy should be interrupted and appropriate measures should be taken to treat the dehydration. There have been rare reports of hypokalemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), OSI-774 therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatotoxicity with or without hepatic impairment: Hepatic failure and hepatorenal syndrome (including fatal cases) can occur with OSI-774 treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. Perform periodic liver testing (transaminases, bilirubin, and alkaline phosphatase) during treatment with OSI-774. Increased frequency of monitoring of liver function is required for patients with pre-existing hepatic impairment or biliary obstruction. Withhold OSI-774 in patients without pre-existing hepatic impairment for total bilirubin levels >3 x institutional upper limit of normal (ULN) or transaminases >5 x ULN. Withhold OSI-774 in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. Discontinue OSI-774 in patients whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within three weeks.

Renal insufficiencies: Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia, or concurrent chemotherapy use. In the event of dehydration, particularly in

patients with contributing risk factors for renal failure (*e.g.*, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), OSI-774 therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Withhold OSI-774 in patients developing severe renal impairment until renal toxicity is resolved. Perform periodic monitoring of renal function and serum electrolytes during OSI-774 treatment.

Gastrointestinal perforation: Gastrointestinal perforation (including fatal cases) can occur with OSI-774 treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation. Permanently discontinue OSI-774 in patients who develop gastrointestinal perforation.

Bullous and exfoliative skin disorders: Bullous, blistering, and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal, can occur with OSI-774 treatment. Discontinue OSI-774 treatment if the patient develops severe bullous, blistering or exfoliating conditions.

Myocardial infarction/ischemia: In the pancreatic carcinoma trial, six patients (incidence of 2.1%) in the OSI-774/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, three patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.1%), and one died due to myocardial infarction. The pooled incidence of myocardial infarction/ischemia in the three monotherapy lung cancer studies was 0.2% in the OSI-774 arms and 0.4% in the control arms.

Cerebrovascular accident: In the pancreatic carcinoma trial, seven patients in the OSI-774/gemcitabine group developed cerebrovascular accidents (incidence: 2.5%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents. The pooled incidence of cerebrovascular accident in the three monotherapy lung cancer studies was 0.6% in the OSI-774 arms and 0.9% in the control arms.

Microangiopathic hemolytic anemia with thrombocytopenia: The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the three monotherapy lung cancer studies was 0% in the OSI-774 arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the OSI-774 plus gemcitabine arm and 0% in the control arm.

Ocular disorders: Corneal perforation or ulceration can occur with OSI-774 treatment. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with OSI-774 treatment and are known risk factors for corneal ulceration/perforation. Interrupt or discontinue OSI-774 therapy if patients present with acute/worsening ocular disorders such as eye pain.

Embryo-fetal toxicity: Based on its mechanism of action, OSI-774 can cause fetal harm when administered to a pregnant woman. When given during organogenesis, OSI-774 administration

resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If OSI-774 is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 2 weeks after the last dose of OSI-774. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking OSI-774.

8.1.2 **ONALESPIB (AT13387) (NSC 749712)**

Chemical Name: **(**2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-1,3-dihydro-isoindol-2-yl]-methanone, *L*-lactic acid salt

Other Name: AT13387AU, Onalespib

Classification: Heat shock protein 90 (HSP90) inhibitor

Molecular Formula: $C_{24}H_{31}N_3O_3.C_3H_6O_3$ **M.W.:** 499.61

Mode of Action: AT13387 is a synthetic non-ansamycin small molecule that inhibits heat shock protein 90 (HSP90. HSP90 seems to affect multiple aberrant signaling pathways and therefore may be of clinical benefit in several cancer treatments.

How Supplied: AT13387 is supplied by Astex Pharmaceuticals Inc. and distributed by CTEP, NCI as a 265 mg free base equivalent (L-lactic acid salt) vial, containing white to off-white lyophilized powder. The agent is formulated in **pH 5.0 (red cap).**

Preparation: Reconstitute the 265-mg lyophilized powder with 10 mL of Sterile Water for Injection (SWFI) resulting in 25.7 mg/mL concentration (10.3 mL total volume). A sticky mass will be formed. Vigorously shake the vial. Agitate until the contents are fully dissolved (about 5 minutes). Leave the diluted vial at ambient temperature for 15-30 minutes to allow any foam to dissipate. If not used immediately, store the reconstituted vial(s) at 2^0 to 8^0 C not to exceed 8 hours.

Withdraw the calculated dose of AT13387 and further dilute it in 250 mL of D5W or 0.9% NS. The prepared IV solution is compatible in PVC or non-PVC infusion bags.

Store the prepared IV solution at 2^0 to 8^0 C not to exceed 8 hours if not used immediately. When removed from the refrigerator, allows the prepared IV solution to sit at room temperature between 15 to 30 minutes before administering to patients. The prepared IV solution must be used within 8 hours -i.e., from the time the drug vial is diluted to the time the IV administration is complete. Protection from light during the infusion period is not required.

Storage: Store the intact vials at 15^0 to 25ºC (59 to 77ºF). Protect from light.

If a storage temperature excursion is identified, promptly return AT13387 to 15^0 to 25ºC (59 to

77ºF) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life surveillance of the intact vials is ongoing**.**
Route of Administration: Intravenous

Method of Administration: Infuse over 1 hour through a central line or a well-defined peripheral vein (Note: an in-line filter is NOT required). If use a peripheral line, be sure to aspirate venous blood prior to starting the infusion. Check the infusion site every 15 minutes. Change infusion site should evidence of swelling or discoloration is observed.

Potential Drug Interactions: AT13387 is a substrate of UGT with a relatively low affinity for UGT isoforms. In vitro data demonstrate that AT13387 is a weak inhibitor of UGT1A1, UGT1A3 and UGT1A9. AT13387 is also a weak inhibitor of CYP1A2, -3A4, -2D6, -2C9 and -2C19. AT13387 appears to metabolize via the glucuronidation, sulphation and N-oxidation.

Pre-clinical studies suggest that AT13387 is a substrate of P-gp, the efflux ratios was above 2 (ranging from 3.4 to 4.6); a moderate inhibitor of BCRP (35.9% +/- 2%, p=0.0001) and P-gp (31.3% +/- 1.2%, p= 0.0009), and a strong inhibitor of MATE1 (94.6% +/- 0.2%, p=0.0001) and MATE2-K (91.2% +/- 1.2%, p= 0.0002).

Patient Care Implications: There are no genotoxicity, carcinogenicity, developmental and reproductive studies conducted with AT13387. Women of childbearing potential should not become pregnant or breastfeed and men should not father a child during the study. All subjects must use acceptable contraceptive measures during the treatment of AT13387 and 3 months after the last dose of the investigational drug.

Systemic infusion reactions (e.g., vomiting, itching skin, or swelling), slow the infusion and/or administer NS or D5W through a "Y" connector in parallel to AT13387 IV infusion. Pre-medication (e.g., dexamethasone, H-1 and H-2 antagonist) may be given before subsequent infusions and/or administer additional volume of 500 mL over 1 hour if medically appropriate.

Avoid extravasation. For local irritation, apply cold compress or topical pain medication.

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Confirmation of the subject's enrolment onto the study is required for agent initial supplies.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3.3 Investigator Brochures - The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-

ctep.nci.nih.gov/iam/

- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative Studies include an **optional** core biopsy before treatment with erlotinib and onalespib, 48-72 hours after cycle 2, day 15 and at progression for the correlates outlined below. Plasma for cfDNA and pharmacokinetic studies will also be performed. Optional core biopsies should only be performed in patients where tissue can be accessed safely and feasibly.

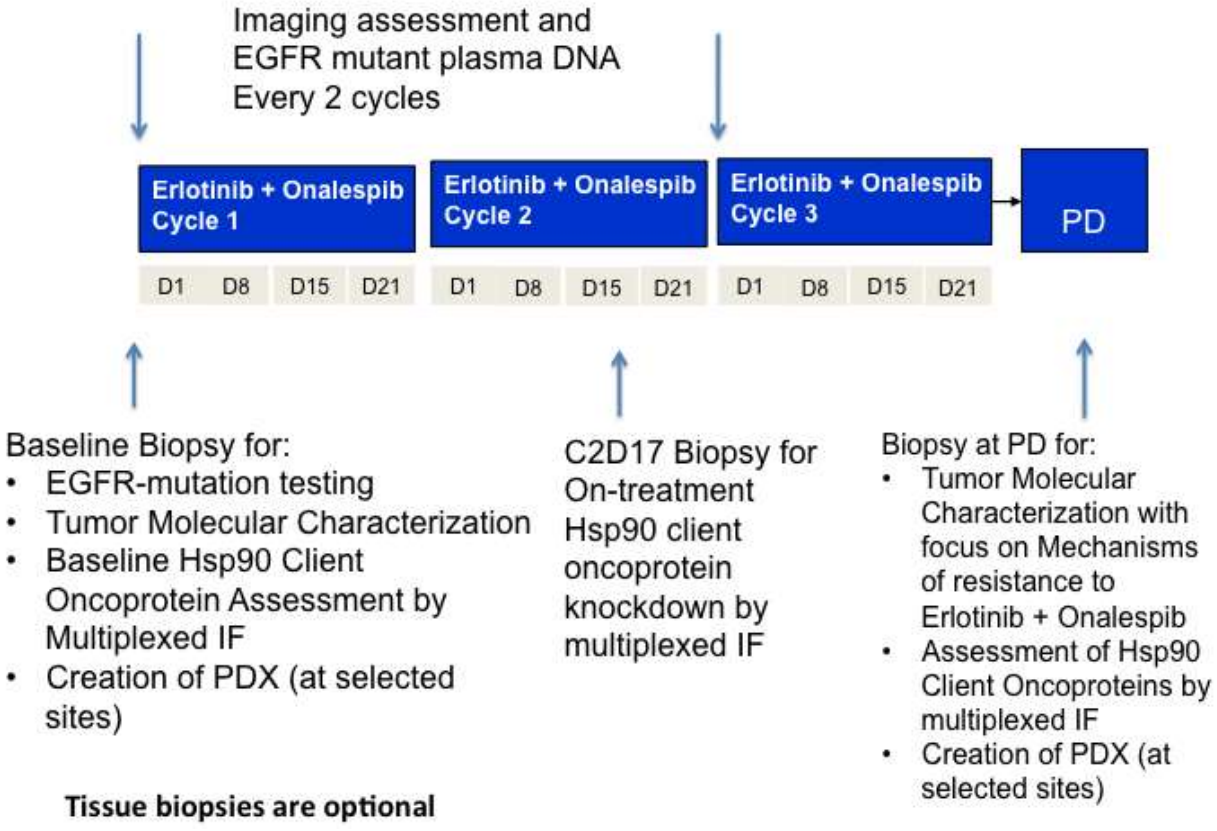


Figure: Timing of correlative tissue and plasma studies. Note: Biopsies are optional for patients in study. Optional biopsies will be obtained prior to initiation of erlotinib and onalespib, 48-72 hours after cycle 2 D15 onalespib administration and at progression. The order priority for biopsies is presented below.

Table: Tissue Correlative Studies Summary (Priority for Baseline and post-progression Biopsy) C2D15 biopsy will be sent solely for Multiplex Immunofluorescence.

Order Priority[a]	Tissue Correlative Study	Slides[c]	Cell Blocks[b]	Institution
1	EGFR Mutation Testing	5	1	Response Genetics
2	Multiplex	10	1	Mack Lab UC

	Immunofluorescence for Hsp90 Client Oncoprotein			Davis
3	Oncopanel	15[c]	2	Brigham & Women's Hospital Center for Advanced Molecular Diagnostics
4	PDX[d]	Fresh Tissue	N/A	Jackson Laboratory West
Please send remaining FFPE tissue block, or 15 unstained slides if block is unavailable to the California Cancer Consortium Biobank at UC Davis for future research.				
a. Prioritization of tissue use and correlates in order from #1 to #4 for baseline biopsy. Biopsy on or around C2D15 will be sent for Multiplex Immunofluorescence for Hsp90 Client Oncoprotein only. Biopsy at progression will be sent for Oncopanel only. b. Paraffin embedded cell block(s) may be substituted for slides. The sample must contain a minimum of 20% tumor tissue. c. Unstained slides total cut from FFPE blocks at 5 microns thickness. The sample must contain a minimum of 20% tumor tissue. d. At select institutions that are affiliated with Jackson Laboratories for creation of PDX Please see the relevant correlative study sections below for further details regarding proper collection, shipping and handling of specimens.				

9.1 Integrated Correlative Studies

9.1.1 *EGFR Mutation Analysis (Response Genetics)*

9.1.1.1 Collection of Specimen(s)

Tissue samples will be sent to Response Genetics for EGFR-mutation testing. This is a confirmatory central test.

One cell block or 5 unstained slides should be sent to Response Genetics

9.1.1.2 Handling of Specimens(s)

PREPARATION OF TISSUE SLIDES
If the tissue block is unavailable, prepare tissue slides.
• The number of slides to be submitted is five (5) 10-micron sections plus three (3) 5-micron sections.
• Positively charged frosted ended slides must be used.

• Section a single section containing tissue onto each slide.
• Sections must be from the same tissue block.
• Subject identifier, and block number must be written legibly in pencil on the frosted end of the slide.
• Slides must not be baked or melted.
• Cover slips must not be used.
• Sections must not be stained.
• Place slides in slide box.

9.1.1.3 Shipping of Specimen(s)

Shipping Address:

Response Genetics
Pharmaceutical Services
1640 Marengo Street
Suite 410
Los Angeles, CA 90033

9.1.1.4 Site(s) Performing Correlative Study

Response Genetics

9.1.2 *Guardant 360 cfDNA Assay*

9.1.2.1 Collection of Specimen(s)

Collect two 10mls of whole blood are collected in Streck Cell-Free DNA Blood Collection (Streck) tubes, which contain a proprietary formaldehyde-free preservative in that stabilizes white blood cells, preventing the release of genomic DNA and allowing shipping and stability for seven days without need for refrigeration, cold bricks or preliminary centrifugation prior to shipping.

9.1.2.2 Handling of Specimens(s)

Mix by gentle inversion 8 to 10 times. Complete the provided barcode label with patient's name, DOB and collection date. Place a barcode label on each tube with barcode in the vertical position. Place blood tubes into foam packaging. Place foam with tubes into specimen bag, close securely and put into the provided shipping box on top of one of the gel packs. (Do not freeze gel packs, use at room temperature). Place test requisition form into outer pocket of the specimen bag. Place the second gel pack on top of the specimen bag and close the shipping box. Place the completed specimen kit into a pre-printed FedEx Clinical Pak and call FedEx for a pick-up. The kit should be kept at room temperature during preparation, while awaiting shipping pick-up and during transit.

9.1.2.3 Shipping of Specimen(s)

The shipping is pre-paid by Guardant Health and shipping label is pre-printed for Overnight Delivery.

9.1.2.4 Site Performing Correlative Study

Guardant Health

9.1.3 *Pharmacokinetics of onalespib*

9.1.3.1 Collection of Specimen(s)

Blood specimens (3 mL whole blood collected in heparinized tubes (Li) sufficient to provide a minimum of 1 mL of plasma) for PK will be collected from patients on day C1D8 of onalespib administration. The timing of start of onalespib infusion should be within 30 min of erlotinib intake on that day (timing of both erlotinib intake and start of onalespib infusion should be recorded). Blood samples for PK should be drawn at time 0 (immediately prior to start of onalespib infusion), then at 0.5 hr (± 5 min), 1 hr (to coincide with immediately at the end of onalespib infusion ±2 min), 2 hr (±5 min), 3 hr (± 5 min), 4 (± 5 min), 6 (± 5 min), 8-9 hr, and 24 hours (this sample falls on the next day) hours post start of onalespib infusion.

Pharmacokinetic Sample Collection Schedule

Sample Number	Day of Collection	Planned Collection Time Relative to onalespib Infusion* (hours)
1	C1D8	0 (Pre onalespib infusion)
2		0.5
3		1 (Immediately at the end of onalespib infusion)
4		2
5		3
6		4
7		6
8		8-9
9	C1D9	24 (post start of onalespib infusion)

* Infusion should start within 30 min of erlotinib intake for that day. Time for erlotinib intake and start of onalespib infusion should be recorded.

9.1.3.2 Handling of Specimens(s)

1. Obtain at least 3 mL of blood into Lithium Heparin (Green Top) Vacutainer tube. Allow enough time for the tube to fill sufficiently.
2. Gently invert the tube for 30 seconds to ensure proper mixing.
3. Place tube on a standard blood roller for a minimum of 5 minutes. If a blood roller

is not available continue to invert the tube further 8-10 times.
4. Centrifuge the tube at 1100 - 1500g for 10-15 minutes at 4-8°C within 1 hour of sample collection.
5. Pipette off the plasma layer (using the pipette provided with the kit)
6. Introduce roughly equal proportions of the plasma into the 2 (primary and secondary) cryovial tubes (size 2 mL).
7. Discard the Lithium Heparin tube per your local policy.
8. Freeze the 2 aliquots of plasma at -70°C or less until shipment to the bioanalytical lab (instructed by Astex).

9.1.3.3 Shipping of Specimen(s)

BASi
2701 Kent Avenue
West Lafayette, IN
47906

Send an electronic manifest to samples@basinc.com along with the tracking information.

9.1.3.4 Site(s) Performing Correlative Study

Astex Pharmaceuticals / BASi

9.2 Exploratory/Ancillary Correlative Studies

9.2.1 *Tumor Molecular Characterization (Oncopanel)*

This targeted cancer next generation sequencing assay (Oncopanel) detects somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples. This clinically validated assay surveys exonic DNA sequences of 300 cancer genes and 113 introns across 35 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. Sequencing results are analyzed and filtered using an in-house developed bioinformatics pipeline and variant calls are further reviewed by a laboratory scientist and molecular pathologist for technical quality and biologic relevance. Results are reported in a tiered format reflecting clinical actionability. Overall, the assay provides an average of 187 fold read depth and is successful in >96% of samples run. In general, this assay is sensitive to 10% mutant allelic fraction (AF) but can detect mutant AF down to 3%; low AF calls are made at the discretion of the reviewing scientists and pathologists.

9.2.1.1 Collection of Specimen(s)

Completion of both assays requires a total of 15 unstained slides cut from FFPE blocks at 5 microns thickness. Hematoxylin and eosin staining will be performed on one slide upon receipt at BWH.

9.2.1.2 Handling of Specimens(s)

The sample must contain a minimum of 20% tumor tissue. Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample.

Specimens will be identified with the NCI Protocol number (P9898), Patient Accession ID, Specimen Name (e.g., tissue), Specimen Number, Date, and Time and alphanumeric identifier for serial samples (e.g., T0, T1, T2 …).

9.2.1.3 Shipping of Specimen(s)

Brigham & Women's Hospital
Center for Advanced Molecular Diagnostics
Shapiro 5054
75 Francis Street
Boston, MA 02115

9.2.1.4 Site(s) Performing Correlative Study

Brigham & Women's Hospital
Center for Advanced Molecular Diagnostics

9.2.2 Patient Derived Xenotransplants (Institutions with agreements with Jackson Laboratory assuring collaborator rights).

9.2.2.1 Collection of Specimen(s)

Tissue for PDX should only be obtained at procedures performed on a Monday, Tuesday, Wednesday, or Thursday. The fresh specimen will be submitted directly and immediately to The Jackson Laboratory using the following procedures.

a. The physician should obtain the maximum amount of tumor that is prudent at the time of biopsy or resection. Minimum sample size is a core measuring 8mm x3mm. Please approximate these dimensions.

b. The specimen should be collected following Institution Universal precautions SOPs for maintaining tissue integrity. Please remind all personnel that are involved in processing the sample that it will be implanted in profoundly immune deficient mice, which is why it is imperative that extra care be taken in sample collection to minimize the risk of transferring human bacteria to the mice.

9.2.2.2 Handling of Specimens(s)

The tumor sample should be placed in a 50 ml screw cap conical tube containing 40 ml RPMI

buffer (without fetal calf serum); preferably within 30 minutes of tumor removal. Seal cap tightly with Parafilm. Sample should be refrigerated at 4°C until packed for shipping on the same day as procurement.

9.2.2.3 Shipping of Specimen(s)

The sealed conical tube containing RPMI & the tumor specimen must be wrapped in absorbent material (i.e. paper towels) and placed in an airtight plastic bag (i.e. a ziplock bag). Pack the specimen into an insulated Styrofoam shipper with a refrigerated (4° C) cool pack (not frozen) to protect specimen from temperature fluctuations. All paperwork pertaining to the patient should be placed in a plastic bag, sealed tightly, and packed with the tissue shipment. Include the Jackson Laboratory Sample Submission Form.

Ship by Fed Ex for overnight delivery to:

The Jackson Laboratory
In Vivo Services
c/o Margaret Bundy or James Keck 1650 Santa Ana Ave.
Sacramento, CA 95838

Prior to shipping, contact for sample coordination: Margaret Bundy 916-469-2609.

9.2.2.4 Site(s) Performing Correlative Study

The Jackson Laboratory

9.2.3 Banking of FFPE tissue for future correlative studies

9.2.3.1 Collection of Specimen(s)

Any remaining FFPE tumor tissue from archival and/or pre-treatment biopsy, and progression biopsy (if available) should be submitted to the California Cancer Consortium Biobank at UC Davis to be accessioned and stored for future research. All submissions must be accompanied by a completed CCC specimen submission form (to be obtained on the CTSU website) and a copy of the corresponding pathology report.

9.2.3.2 Handling of Specimens(s)

Ideally, 1-2 paraffin-embedded tissue blocks containing formalin-fixed tumor, processed according to standard institutional protocols, will be submitted. If blocks are unavailable, 15 unstained slides will be accepted as an alternative. Tissue should be cute at 5 microns and mounted on positively charged (+) slides.

9.2.3.3 Shipping of Specimen(s)

All FFPE tissue for banking should be sent at ambient temperature. For summer shipments,

please include a room temperature cool pack to insulate the specimen and protect paraffin from melting. Specimens should be shipped to the following address:

Dr. Philip Mack/ Anthony Martinez
UC Davis Comprehensive Cancer Center
4501 X Street, Suite 1009
Sacramento, CA 95817
Phone: 916-734-6447
Email: axmartinez@ucdavis.edu or pcmack@ucdavis.edu

Please notify the bank at the time of shipping via email (axmartinez@ucdavis.edu)

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 7 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the first cycle of therapy. For subsequent cycles, laboratory evaluations should be conducted within 72 hours prior to initiation of therapy.

		Cycle 1				Cycle 2				Cycle 3 (and subsequent cycles)				
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[c]
Erlotinib		X----------											----------X	
onalespib[n]		X	X	X		X	X	X		X	X	X		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											----------X	
History and Physical exam	X	X		X		X		X		X		X		X
Vital signs	X	X		X		X		X		X		X		X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a, m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PTT/INR[k]	X													
EKG (and as indicated[l])	X													
Echocardiogram or MUGA	X													
Adverse event evaluation		X----------											----------X	X
Tumor measurements	X	Tumor measurements are repeated every *2 cycles* (8 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every 8 weeks (+/- 7 days) (~2 cycles).												X
Brain Imaging[h]	X													
B-HCG	X[b]													
EGFR Mutation Testing	X[d]													
Oncopanel (NGS)[g]	X													X
Pharmacokinetic Studies			X[e]											
Plasma cfDNA	X[f]									X[f]				X[f]
Multiplex Immunofluorescence of Hsp90 Client Oncoproteins[i]	X						X							X
Tissue for PDX[j]	X													X

A: Erlotinib: Dose as assigned; *PO daily continuous. Each cycle is 28 days in length.*
B: Onalespib: Dose as assigned*; IV every Day 1, 8, 15. Each cycle is 28 days in length.*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation. Patients will then be followed every 12 weeks for 1 year then annually. Please see Section 5.6 for further details..
d: Optional biopsy for EGFR mutation. See section 9 of protocol for further details.
e: Blood samples for PK analysis will be obtained at C1D8. See section 9 of protocol for further details.
f: Collect blood for cfDNA prior to treatment and every 2 cycles. Draw venous blood into two (2) 10 mL Streck tubes and immediately gently invert the tubes 8-10 times. See section 9 of protocol for further details.
g: Optional studies on biopsied tissue before initiation of erlotinib and onalespib obtained by fresh biopsy.
h. Brain imaging required prior to treatment. Untreated brain metastases are not allowed per protocol, but patients with treated brain metastases are allowed. MRI brain or CT head is acceptable. Contrast enhanced scans are suggested unless contraindicated.
i. Optional biopsy prior to treatment and 48-72 hours after administration of onalespib cycle 2 day 15 (cycle 2 day 17, and within 4 weeks of demonstration of progressive disease.
j. Only at institutions with affiliation with Jackson Laboratories for creation of PDX.
k. Patients taking warfarin or other coumarin-derivative anticoagulants should have more frequent INR/PT determinations on study (once a week for the first month on treatment and then as clinically indicated not less than once per cycle (28 days) and then once a week for a minimum of 2 weeks following discontinuation of Erlotinib).
l. Mean resting corrected QT interval on 3 separate EKGs (QTc using Fredericia's formula (QTcF)) > 470 msec (See Appendix E for Fridericia's formula). Additional EKGs on study not required but may be performed at the treating investigators discretion.
m. Window for laboratories after initiation of treatment is within 72 hours of subsequent treatment.
n. Window of 48 hours permitted for onalespib dosing.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs in combination has not yet been established in the patient population being studies, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *8* weeks.

Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks.

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) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *erlotinib and onalespib.*

Evaluable for objective response. Patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. All patients are required to have measurable disease at baseline. 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 re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not

be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of 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 4 weeks before the beginning of the treatment.

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is 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.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy

in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

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

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

Note: 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.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

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

11.1.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive 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, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS (not otherwise specified) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Because Phase 2 Cohort A will include patients who have failed to respond to Erlotinib after up to 6 months on Erlotinib alone, the study will also collect the date of first Erlotinib therapy prior to enrollment.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

See also Section 14 'CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS,' Subsection 14.1 'Oversight.'

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and

statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL *(Note: A DTL is not required for this study).*

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site

registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the

recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase 1/2 trial of Onalespib in combination with erlotinib. The initial segment of the trial will attempt to escalate the starting dose of onalespib, in two steps, when given in combination with a fixed dose of erlotinib. The primary endpoint during dose escalation is dose-limiting toxicity (DLT), as defined in Section 5.2. Dose escalation will follow a 3+3 design, motivated by the desire to limit the incidence of dose-limiting toxicity to the lowest feasible levels. Dose escalation rules are defined in Section 5.3. All patients who receive any amount of study drug will be evaluable for toxicity and reported, but patients must either receive an informative treatment (as defined in Sections 5.2 and 5.3) or experience DLT to be informative about dose escalation decisions.

When the phase 2 dose has been established, recruitment into Phase 2 cohorts A and B will begin simultaneously. Cohort A will enroll patients with EGFR activating mutations (specified above) who have begun erlotinib within the previous 6 months (180 days), and have been evaluated, but without achieving a partial or complete response as defined by RECIST criteria by imaging performed not less than 12 weeks after starting erlotinib. Cohort B will enroll patients with metastatic or recurrent NSCLC that harbor an EGFR exon 20 insertion and have progressive disease on platinum-based chemotherapy. The primary endpoint for the phase 2 segment is best response by RECIST criteria, and each cohort will be independently governed by Simon's two-stage minimax design, implemented to distinguish a 25% response rate from an assumed background rate of 5%, with 10% type I and type II error rates. For each phase 2 cohort, the initial stage will enroll 13 subjects, continuing if one or more respond. The target total accrual in each cohort will be 20 subjects, with 3 responses considered encouraging for further development in the relevant class of patients.

13.2 Sample Size/Accrual Rate

The phase 1 segment of the trial is expected to enroll between 12 and 18 subjects, with a worst-case scenario requiring 24 informative subjects. The Phase 2 segment is expected to require 40 subjects (20 per cohort) but could stop for futility with 26 total subjects. The target sample size is thus 46, allowing for 6 subjects from phase 1 at the RP2D to be included in one or the other Phase 2 cohort. The likely range of sample size is from 32 to 52.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	4	3	0	0	**7**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	2	1	0	0	**3**
White	16	14	4	2	**36**
More Than One Race	0	0	0	0	**0**
Total	**22**	**18**	**4**	**2**	**46**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Stratification Factors

Eligible patients will be classified in one of two possible strata: (A) patients with EGFR activating mutations who have been treated with erlotinib; or (B) patients will metastatic or recurrent NSCLC that harbor an EGFR exon 20 insertion and have progressive disease on platinum-based chemotherapy. The strata are pooled during the dose-escalation segment, but eligible stratum A patients will have progressed on erlotinib. In phase 2, the strata are enrolled as separate cohorts, and stratum A patients are eligible if they have not responded to erlotinib.

13.4 Analysis of Secondary Endpoints

Tumor response is the primary endpoint for phase 2, but secondary for phase 1. The phase 2 results will be reported with respect to the Simon's two-stage design, including any relevant patients from phase 1, of the same stratum, treated at the RP2D. If there is a response at a lower dose, the report will be supplemented with isotonic regression estimates. Because stratum A includes subjects who have progressed on erlotinib, as well as subjects who have neither progressed nor responded after at least 12 weeks on erlotinib, results for these two groups will be reported separately as a secondary data summary. A significant difference (two-sided 0.10 level) in response rates is not expected, but it would imply a significant number of responses in at least one sub-group, and any response after progression on erlotinib would be an interesting finding.

PFS is a secondary endpoint, and will be summarized for stratum B as time from first protocol treatment, using the product-limit (Kaplan-Meier) estimator. For stratum A, the product-limit estimate of PFS will be calculated separately for second-line patients, who have progressed on erlotinib. For patients in stratum A who have not yet progressed on erlotinib, the time on pre-protocol erlotinib and PFS on protocol therapy will be displayed as event time-lines, and any Kaplan-Meyer plot using the combined data for stratum A will use left truncation, to avoid

crediting the combination with the progression-free time required to enter the study.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

Adverse events from all patients will be reported from the time of their first treatment with protocol agents. . Replacement of patients for dose escalation decisions is described in Section 5.3.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria and received no study medication will be included in the main analysis of the response rate. Patients in response categories 4-8 will be considered to have a treatment failure (analyzed as if disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

Phase 2 conclusions will be based on all eligible patients treated at the RP2D. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

Analysis of tissue and plasma biomarkers are exploratory in nature, constrained by the sample size requirements of a phase 1/2 trial, and availability of biopsies. For circulating DNA, the Guardant panel will provide an opportunity to observe loss of stratum-defining markers after treatment. Such loss-of-signal events will be cross-classified with best response and summarized with changes in tumor measurements. Strong association between loss of marker signal (including plasma EGFR-T790M) and response may provide preliminary indication of potential as a predictive marker. Emergent markers will be similarly evaluated as potential predictors of treatment resistance, and the mutation profile of responding patients will be examined informally for repeating patterns. Multiplexed immunofluorescence in paired tumor biopsies will be used to demonstrate the knockdown of Hsp90 client oncoproteins. Analysis will similarly involve association of knockdown and tumor response or measurements. Biopsies are optional. Because any observation of target knock-down is an informative observation,

biopsies will continue to be sought, even if the initial rate of consent to biopsies is low. If zero out of 6 on-treatment biopsies show target knock-down, the upper 80% confidence bound would be below 25%, and hence inconsistent with the target response rate under assumed mechanisms. We thus regard 6 biopsies as a minimum, if negative. When available, the first 6-paired biopsies will be examined for multiplexed immunofluorescence. Failure to observe target knock-down in the first zero out of 6 biopsies will prompt a re-evaluation of performing on-target biopsies in additional patients enrolled on trial.

14. CCC POLICIES FOR MONITORING CONSORTIUM TRIALS

This protocol is monitored at several levels, as described in this section. To summarize: The trial PI has access to the data at all times. The CCC Data Coordinating Center reviews accrual and toxicities monthly. An external, independent DSMC reviews the study progress twice yearly. In addition, for the Phase 1 portion, the study PI will have monthly - and as needed - conference calls with study investigators to review accrual, progress, and any unforeseen issues. Dose escalation/expansion/de-escalation decisions require sign-off by the study PI (or his or her designee) and study statistician (or his or her designee). During the Phase 2 portion, the study PI will have quarterly - and as needed - conference calls with study investigators to review accrual, progress, and any unforeseen issues. Decisions to proceed to the second stage of the Phase 2 trial will require sign-off by the study PI and (the trial statistician).

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase 2 trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7.0) and electronic case report forms. The Data Coordinating Center for the CCC Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCC that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCC initiated trial on the CCC website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase 1 trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
(b) for Phase 2 trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized

logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCC teleconference meeting for review and approval.

14.1 Oversight

Oversight of the conduct of CCC trials occurs at several levels:

1. The Data Coordinating Center for the CCC flags all trials that are approaching a decision in terms of toxicity (for both Phase 1 and Phase 2 trials) or responses (for Phase 2 trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism or his or her designee, and are communicated to the participating centers by the CCC Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase 1 trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCC institution; this audit is initiated by CTEP.

3. An independent CCC DSMC will review CCC trials every 6 months. This DSMC will consist of 6 voting members (3 medical oncologists or hematologists involved in Phase 1/2 cancer clinical trials but not participating in CCC studies, a patient representative and a statistician) and a non-voting CCC statistician.

a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
b. This DSMC will review each CCC trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.
c. The DSMC will report to the CCC leadership.

REFERENCES

1. Wu, Y.L., et al., *Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial.* The lancet oncology, 2013. **14**(8): p. 777-86.
2. Sequist, L.V., et al., *Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors.* Science translational medicine, 2011. **3**(75): p. 75ra26.
3. Takezawa, K., et al., *HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation.* Cancer discovery, 2012. **2**(10): p. 922-33.
4. Erlotinib Investigator's Brochure, *OSI Pharmaceuticals, Inc., Genentech, Inc., and F. Hoffman-La Roche Ltd. 13th Edition.* 2009.
5. Mok, T.S., et al., *Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.* The New England journal of medicine, 2009. **361**(10): p. 947-57.
6. Rosell, R., et al., *Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.* The lancet oncology, 2012. **13**(3): p. 239-246.
7. Sequist, L.V., et al., *Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2013. **31**(27): p. 3327-34.
8. Miller, V.A., et al., *Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial.* The lancet oncology, 2012. **13**(5): p. 528-38.
9. Lecia V. Sequist, J.-C.S., Shirish M. Gadgeel, Heather A. Wakelee, D. Ross Camidge, Andrea Varga, Benjamin J. Solomon, Vassiliki Papadimitrakopoulou, Sarah S. Jaw-Tsai, Lisa Caunt, Paramjit Kaur, Lindsey Rolfe, Andrew R. Allen, Jonathan Wade Goldman, *First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M).* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2014. **32**(5s): p. suppl; abstr 8010.
10. Pasi A. Janne, S.S.R., James Chih-Hsin Yang, Myung-Ju Ahn, Dong-Wan Kim, Sang-We Kim, David Planchard, Yuichiro Ohe, Enriqueta Felip, Claire Watkins, Mireille Cantarini, Serban Ghiorghiu, Malcolm Ranson, *Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC).* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2014. **32**(5s): p. suppl; abstr 8009.
11. Trepel, J., et al., *Targeting the dynamic HSP90 complex in cancer.* Nature reviews. Cancer, 2010. **10**(8): p. 537-49.
12. Shimamura, T., et al., *Hsp90 inhibition suppresses mutant EGFR-T790M signaling and overcomes kinase inhibitor resistance.* Cancer research, 2008. **68**(14): p. 5827-38.
13. Graham, B., et al., *The heat shock protein 90 inhibitor, AT13387, displays a long duration of action in vitro and in vivo in non-small cell lung cancer.* Cancer science, 2012. **103**(3): p. 522-7.
14. Keisha Hearn, T.S., Jon Lewis, Vanessa Martins, Neil Thompson, Mohammad Azab,

John Lyons, Nicola G. Wallis, *The HSP90 inhibitor, AT13387, displays single agent activity in erlotinib-sensitive and -resistant models of EGFR-activated NSCLC.* World Congress on Lung Cancer, 2013: p. P1.05-012.

15. Tomoko Smyth, J.L., Keisha Hearn, Neil Thompson, John Lyons, Nicola G. Wallis, *The HSP90 inhibitor, AT13387, combined with erlotinib improves response in EGFR-driven xenograft models of NSCLC.* AACR Annual Meeting, 2014: p. 1794.
16. Bean, J., et al., *MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib.* Proceedings of the National Academy of Sciences of the United States of America, 2007. **104**(52): p. 20932-7.
17. Yasuda, H., S. Kobayashi, and D.B. Costa, *EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications.* The lancet oncology, 2012. **13**(1): p. e23-31.
18. Xu, W., et al., *Sensitivity of epidermal growth factor receptor and ErbB2 exon 20 insertion mutants to Hsp90 inhibition.* British journal of cancer, 2007. **97**(6): p. 741-4.
19. Chen, Z., et al., *A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response.* Nature, 2012. **483**(7391): p. 613-7.
20. Gandara, D.R., et al., *Bridging tumor genomics to patient outcomes through an integrated patient-derived xenograft platform.* Clinical lung cancer, 2015. **16**(3): p. 165-72.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drugs AT13887 and Erlotinib. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Erlotinib interacts with a certain specific enzyme in your liver.

- The enzyme in question is CYP3A4 and erlotinib is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Erlotinib and/or onalespib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Erlotinib must be used very carefully with other medicines that use certain ***CYP3A4 to be effective or to be cleared from your system.*** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***strong inducers of CYP3A4.***

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.

- Your prescribers should look at this web site http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- If you drink grapefruit juice or eat grapefruit or Seville oranges: Avoid these until the study is over.
- Do not take omeprazole (also known as Prilosec) for heartburn or for stomach reflux. Talk to your doctor or pharmacist before taking it.
- If use ranitidine, cimetidine, or famotidine for heartburn, erlotinib must be taken 10 hours after these drugs and at least 2 hours before the next dose of ranitidine, cimetidine, or famotidine. Talk to your doctor or pharmacist.
- If use antacids, take the antacid dose several hours from erlotinib dose.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking erlotinib and onalespib.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drugs erlotinib and AT13387 (Onalespib lactate). This clinical trial is sponsored by the NCI. Erlotinib and AT13387 (Onalespib lactate).may interact with drugs that are ***processed by your liver***. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Erlotinib interacts with a ***specific liver enzyme called CYP3A4*** and must be used very carefully with other medicines that interact with ***CYP3A4.***

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***strong inducers/inhibitors of CYP3A4.***
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

CTEP-assigned Protocol # 9987
Consortium Protocol Phl-80
Local Protocol # _____

APPENDIX C PATIENT'S MEDICATION DIARY

Today's date _____ **Cycle Number:** _____ **Agent: Erlotinib**

Patient Name_____(*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take **Erlotinib tablets by mouth once a day (in the morning)**. You should take the tablets on an empty stomach at 1 hour before food or 2 hours after a meal. Take with 1 cup (200 mL) of water. Tablets should be swallowed whole, do not chew or crush If you have a G-tube, your study doctor will provide you with specific instructions for administration of erlotinib. If you miss a dose and do not take it within 6 hours of the usual time of your morning dose, skip the dose and resume taking Erlotinib the next morning. Please contact your doctor if you have any questions.
   Dose: take _____ x _____ mg tablet(s).
3. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of Erlotinib tablets when you return for each appointment.

Day	Date	Time of dose	Erlotinib # of tablets taken _____**mg**	**Comments**
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient Signature: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
3. Total number of tablets taken this month **Erlotinib**_____ _____
4. Physician/Nurse/Data Manager's Signature _____

APPENDIX D DRUGS WITH KNOWN RISK OF TORSADES DE POINTES

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)
Astemizole (Removed from US Market)	Hismanal®	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection
Bepridil (Removed from US Market)	Vascor®	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen®	Antimalarial	Malaria
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection
Cisapride (Removed from US Market)	Propulsid®	GI stimulant	Increase GI motility
Citalopram	Celexa®, Cipramil®	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart rhythm
Domperidone (On non US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Antinausea	Nausea, vomiting
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq®	Antiarrhythmic	Abnormal heart rhythm

Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Antiarrhythmic	Abnormal heart rhythm

Fluconazole	Diflucan®, Trican®	Antifungal	Fungal infection
Gatifloxacin (Removed from US Market)	Tequin®	Antibiotic	Bacterial infection
Grepafloxacin (Off market worldwide)	Raxar®	Antibiotic	Bacterial infection
Halofantrine	Halfan®	Antimalarial	Malaria
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Antipsychotic	Schizophrenia, agitation
Ibutilide	Corvert®	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin®, Tavanic®	Antibiotic	Bacterial infection
Levomethadyl (Removed from US Market)	Orlaam®	Opioid agonist	Narcotic dependence
Mesoridazine (Removed from US Market)	Serentil®	Antipsychotic	Schizophrenia
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox®, Avalox®, Avelon®	Antibiotic	Bacterial infection
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®,	Antiemetic	Nausea, vomiting

	Setronax®		
Pentamidine	Pentam®	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap®	Antipsychotic	Tourette's Disorder
Probucol (Removed from US Market)	Lorelco®	Antilipemic	Hypercholesterolemia
Procainamide (Oral off US mkt)	Pronestyl®, Procan®	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan®, Propoven®	Anesthetic, general	Anesthesia
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Antiarrhythmic	Abnormal heart rhythm
Sevoflurane	Ulane®, Sojourn®	Anesthetic, general	Anesthesia
Sotalol	Betapace®, Sotalex®, Sotacor®	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (Removed from US Market)	Zagam®	Antibiotic	Bacterial infection
Sulpiride (On non US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from US Market)	Seldane®	Antihistamine	Allergic rhinitis
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa®	Anticancer	Cancer (thyroid)

APPENDIX E FRIDERICIA'S CRITERIA FOR QTC CALCULATION

Fridericia's formula QTcF = (QT/RR^0.33). RR is the time from the interval of 1 QRS complex to the next measured in seconds and is commonly calculated as (60/HR) (Hosmane et al, Journal of Applied Research 2006).

APPENDIX F SPECIMEN COLLECTION FOR PHARMACOKINETIC STUDIES FOR PHI-80 (NCI# 9878)

Title: A Phase 1/2 Trial of Erlotinib and Onalespib lactate in EGFR-Mutant Non-Small Cell Lung Cancer

At each protocol specified time, draw and collect 3 ml blood in heparinized (green top) tube. Start prior to Onalespib dosing on cycle 1, day 8. Blood specimens (3 mL whole blood collected in heparinized tubes (Li) sufficient to provide a minimum of 1 mL of plasma) for PK will be collected from patients on day C1D8 of Onalespib administration. The timing of start of onalespib infusion should be within 30 min of erlotinib intake on that day (timing of both erlotinib intake and start of Onalespib infusion should be recorded).

Handling of Specimen
1. Obtain at least 3 mL of blood into Lithium Heparin (Green Top) Vacutainer tube. Allow enough time for the tube to fill sufficiently.
2. Gently invert the tube for 30 seconds to ensure proper mixing.
3. Place tube on a standard blood roller for a minimum of 5 minutes. If a blood roller is not available continue to invert the tube further 8-10 times.
4. Centrifuge the tube at 1100 - 1500g for 10-15 minutes at 4-8°C within 1 hour of sample collection.
5. Pipette off the plasma layer (using the pipette provided with the kit)
6. Introduce roughly equal proportions of the plasma into the 2 (primary and secondary) cryovial tubes (size 2 mL).
7. Discard the Lithium Heparin tube per your local policy.
8. Freeze the 2 aliquots of plasma at -70°C or less until shipment to the bioanalytical lab (instructed by Astex).

Pharmacokinetic Sample Collection Schedule

Title: A Phase 1/2 Trial of Erlotinib and Onalespib lactate in EGFR-Mutant Non-Small Cell Lung Cancer

Patient's Initials _____ _____ Patient ID # _____ _____
(first) (last)

Study Site _____ Height _____ cm Weight: ____ . ____ kg BSA ____ . ____ ____ m^2

Erlotinib Dose _____ mg **Start Date/time** _____

Onalespib (AT13387) Dose _____ mg/m^2 IV infusion

Infusion Start Date/time _____ **Infusion End time** _____

Blood samples (at least 3 mL) for PK should be drawn into lithium heparin containing tubes at time 0 (immediately prior to start of onalespib infusion), then at 0.5 hr (± 5 min), 1 hr (to coincide with immediately at the end of onalespib infusion ±2 min), 2 hr (±5 min), 3 hr (± 5 min), 4 (± 5 min), 6 (± 5 min), 8-9 hr, and 24 hours (this sample falls on the next day) hours post start of onalespib infusion.

Sample Name	Matrix	Planned Collection Time Relative to onalespib Infusion* (hours)	Sample Date (mm:dd:yy)	Expected Time (hh:mm)	Actual Time (hh:mm)	Drawn By (initials)	Comments
P1	Plasma	Pre-ONALESPIB infusion					
P2	Plasma	0.5 hr (± 5 min) after ONALESPIB					
P3	Plasma	1 hr (± 2 min) after ONALESPIB (immediately at end of infusion)					
P4	Plasma	2 hr (± 5 min) after ONALESPIB					
P5	Plasma	3 hr (± 5 min) after ONALESPIB					
P6	Plasma	4 hr (± 5 min) after ONALESPIB					
P7	Plasma	6 hr (± 5 min) after ONALESPIB					
P8	Plasma	8-9 hr after ONALESPIB					
P9	Plasma	24 hr** (post-start of ONALESPIB infusion)					

*Infusion should start within 30 min of erlotinib intake for that day. Time for erlotinib intake and start of onalespib infusion should be recorded.

** 24 hour sample should be taken prior to C1D9 dosing of erlotinib.