For Protocol Amendment 8 of: **NRG-LU003**, "A Biomarker-Driven Protocol for Previously Treated NSCLC ALK Positive Patients: The NCI-NRG-ALK Protocol"

NCI/Local Protocol #: NRG-LU003

NCI Protocol Version Date: January 20, 2022

Request for Rapid Amendment (RRA) for studies using ensartinib and for studies using lorlatinib:

Section	Change
7.3.5	In response to a CTEP Request for Rapid Amendment (RRA) for studies using ensartinib, the following NOTE was added: • NOTE: This study is closed to accrual and patients who received ensartinib are no longer receiving treatment; therefore the CAEPR will not be further updated.
7.3.6	In response to a CTEP Request for Rapid Amendment (RRA) for studies using lorlatinib, the CAEPR for lorlatinib (version 2.2, June 24, 2020) was revised as follows: • Added New Risk: o Rare but Serious: Central nervous system necrosis; Hyperglycemia; Hyperlipidemia o Also Reported on Lorlatinib Trials But With Insufficient Evidence for Attribution: Anorexia; Bronchopulmonary hemorrhage; Cardiac disorders - Other (cardiac tamponade); - Cardiac disorders - Other (left ventricular dysfunction); Chest pain - cardiac; Cholecystitis; Heart failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic function abnormal); Injury, poisoning and procedural complications - Other (traumatic intracranial hemorrhage, intentional self-injury); Ischemia cerebrovascular; Mucositis oral; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (neoplasm progression, pericardial effusion malignant); Nervous system disorders - Other (neurological symptom, carpal tunnel syndrome); Neutrophil count decreased; Palpitations; Pericardial effusion; Sinus bradycardia; Small intestinal obstruction; Surgical and medical procedures - Other (radiotherapy to bone); Vascular disorders - Other (thrombosis); Voice alteration; White blood cell decreased • Increase in Risk Attribution

	○ Changed to Rare but Serious from Also Reported on Lorlatinib Trials But With Insufficient Evidence for Attribution: Hypertension • Decrease in Risk Attribution: ○ Changed to Also Reported on Lorlatinib Trials But With Insufficient Evidence for Attribution from Less Likely: Amnesia; Constipation; Dizziness; Dysarthria; Generalized edema; Headache; Irritability; Myalgia; Nausea; Rash maculo-papular; Serum amylase increased; Vomiting; Tinnitus • Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements: ○ Added: Cognitive disturbance

Other changes:

Section	Change
Global	The version date was updated and punctuation and formatting errors were corrected.
Study Team, Study Champion table, NRG Oncology contact table	• Dr. [redacted] replaced Dr. [redacted] as the SWOG Study [redacted] and SWOG champion; • [redacted] replaced [redacted] • [redacted] phone number was corrected.
Document History table	This amendment was added.
CTSU Contact Information table 8.1 14 14.1 14.4 14.5	These sections were updated per current CTSU/NCI logistics.
2.2	At the end of the 1st sentence, "and for first-line use" has been added because the FDA approved brigatinib as a first-line treatment option for patients with metastatic ALK+ NSCLC.
3.3	The "Prior to Step 2 Registration" subhead was deleted since it is not applicable to every criterion.
4 Pre-treatment table	Reference to the Foundation Medicine specimen labeling instructions was added to the footnote, for clarity.
4 During treatment table	The frequency of the lipid panel for patients receiving lorlatinib was revised as follows to align with the lorlatinib FDA label: From: *For patients receiving lorlatinib only; prior to cycle 1, day 1 to establish baseline*

	to: *for patients receiving lorlatinib only (day 1 of cycles 1-3, and every 3 cycles thereafter)*
5.2.1	A new paragraph was added to define "missed dose," for clarity.
5.4.2	Prohibited therapies for brigatinib were revised to match the FDA label as follows: • Bullet 1 – deleted "or moderate" and added "or inducers" • Bullet 2 – deleted
15.4	Paragraph 4, 1st sentence – the time of the assessment was corrected to after the trial has "accrued 100 patients".
APPENDIX XVI	The PDF Wallet Card was updated to be a fillable form.
Informed Consents	There are no changes to the sample contents for alectinib, brigatinib, ceritinib, crizotinib, ensartinib, pemetrexed, and screening except the version dates were changed to be consistent with the amended protocol. CTEP issued a Request for Rapid Amendment (RRA) for studies using ensartinib, but the risk profile was not revised because the study is closed to accrual and patients who received ensartinib are no longer receiving treatment. For changes to the sample consent for lorlatinib, see the summary of changes attached to that consent.

NRG ONCOLOGY
NRG-LU003
(ClinicalTrials.gov NCT # 03737994)

A BIOMARKER-DRIVEN PROTOCOL FOR PREVIOUSLY TREATED ALK-POSITIVE NON-SQUAMOUS NSCLC PATIENTS: THE NCI-NRG ALK PROTOCOL

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
NRG Oncology
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Study Team (20-JAN-2022)

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Winship Cancer Institute of Emory University [redacted] Emory University Hospital, Room H-184 1364 Clifton Road, NE Atlanta, GA 30322 Phone: [redacted]	NRG Oncology Statistical and Data Management Center & John Hopkins University School of Medicine 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 [redacted] Fax: [redacted]
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The following NCTN Group Study Champion has been added to this trial: (20-JAN-2022)

Allliance for Clinical Trials in Oncology	[redacted] MD
ECOG-ACRIN Medical Group	[redacted] MD, PhD
SWOG	[redacted] MD

NRG Oncology Contact Information (20-JAN-2022)	
Data Management For questions concerning eligibility or data submission	[redacted] and [redacted] NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 [redacted] / [redacted] [redacted]
RT data submission to TRIAD (include if applicable)	Triad-Support@acr.org
Protocol Development: For questions concerning protocol and informed consent versions & amendments	[redacted] NRG Oncology 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 Phone: [redacted] Fax: [redacted] [redacted] *continued*
Lung Cancer Committee [redacted]	[redacted] MD

	[redacted]	

Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Alectinib	PMB	794611	[redacted]	DCTD, NCI
Brigatinib	PMB	784728		
LDK378 (Ceritinib)	PMB	802646		
Ensartinib	PMB	784729		
Lorlatinib	PMB	803411		
Crizotinib	PMB	749005		
Pemetrexed	Commercial	698037		
Cisplatin	Commercial	119875		
Carboplatin	Commercial	241240		

Participating Sites

☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History

	Version Date
Amendment 8	**January 20, 2022**
Amendment 7	August 11, 2020
Amendment 6	June 29, 2020
Amendment 5	February 17, 2020
Amendment 4	November 13, 2019
Amendment 3	September 9, 2019
Amendment 2	June 21, 2019
Amendment 1	May 20, 2019
Pre-activation revision	March 4, 2019
Initial	November 19, 2018

NRG ONCOLOGY

NRG-LU003 (11-AUG-2020)

A BIOMARKER-DRIVEN PROTOCOL FOR PREVIOUSLY TREATED ALK-POSITIVE NON-SQUAMOUS NSCLC PATIENTS: THE NCI-NRG ALK PROTOCOL

CONTACT INFORMATION (20-JAN-2022)		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission. Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU member's website (located at https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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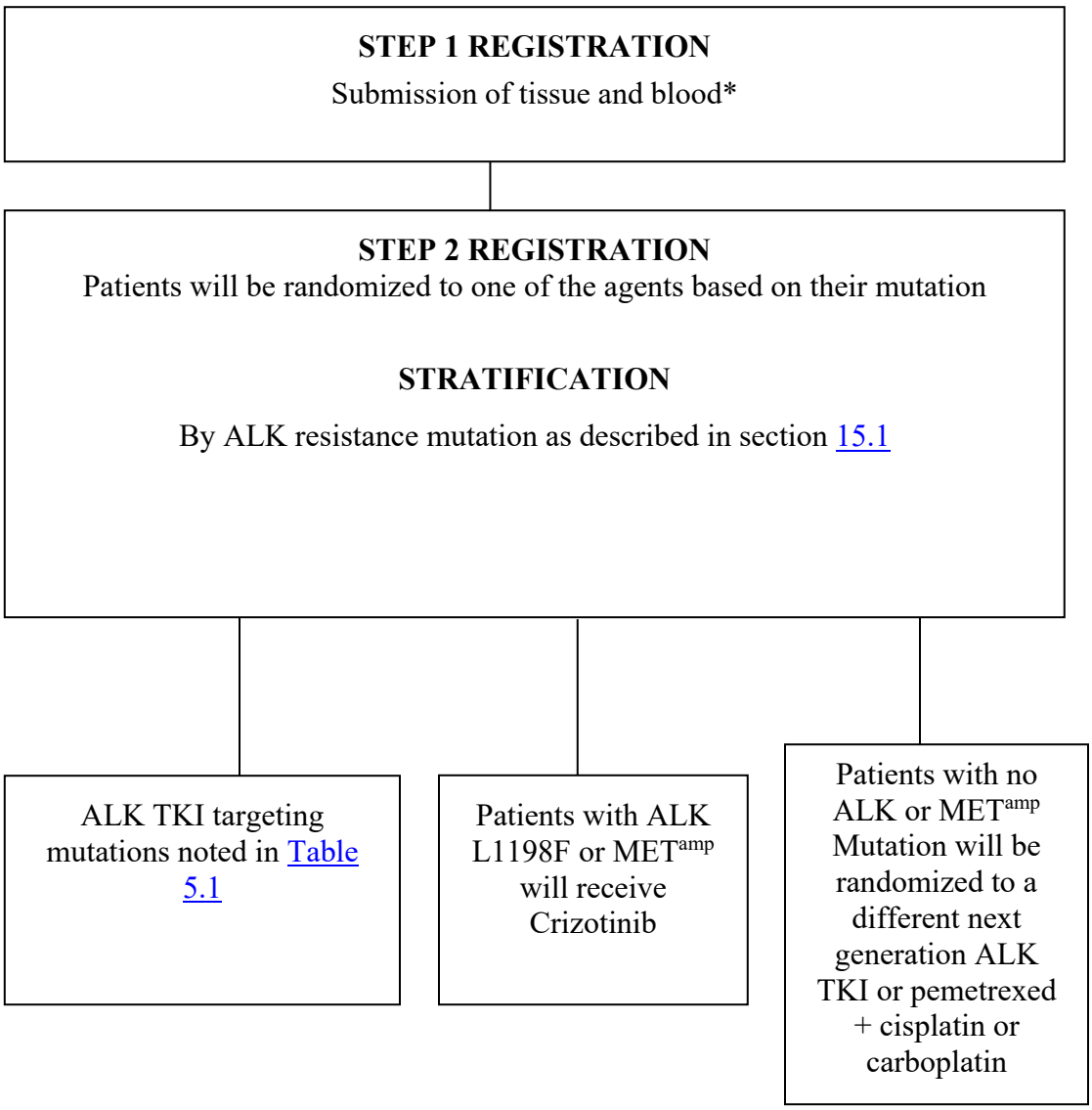
SCHEMA (17-FEB-2020)



*Tissue and blood must be sent after a patient is registered to the study so that an NRG-LU003 patient identifier may be sent with the samples.

Based on the identified ALK mutation(s), patients will be assigned to treatment with the indicated ALK inhibitors as described in Section 5.1 and Section 15.1. If no ALK-resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not received or pemetrexed based chemotherapy.
Next-generation ALK inhibitor = 2nd or 3rd generation

1. OBJECTIVES

1.1 Primary Objective

- To assess whether ALK kinase domain mutations (G1202/C1156Y /I1171/L1196/ V1180/ F1174/ compound mutation) associated with drug resistance are prognostic for objective response to subsequent ALK inhibitor therapy.
- To assess whether subsequent pemetrexed based chemotherapy improves objective response comparing to ALK inhibitor therapy for no ALK mutation patients
- To evaluate objective responses of patients with specific genetic alterations (ALKL1198F/MET double mutation or high-level MET gene amplification) treated with crizotinib.

1.2 Secondary Objectives

- Progression-free survival (PFS)
- Duration of response (DOR)
- Overall survival (OS)
- Intracranial objective response rate (ORR)
- Safety and tolerability

1.3 Correlative Science Objective

- Establish concordance between tumor and liquid biopsies

2. BACKGROUND

Prospective molecular testing for *ALK* rearrangements and therapeutic targeting with small molecule tyrosine kinase inhibitors (TKIs) of ALK inhibitors are now the standard of care for those patients with advanced non-small cell lung cancer (NSCLC) with ALK –rearranged (i.e., ALK-positive). However, the optimal treatment strategy and sequence of these agents for , particularly in the setting of acquired resistance, has not yet been established. Although ALK-positive NSCLC patients live longer due to the availability of ALK targeted therapies, most will eventually relapse and die of the disease.

To date, at least 27 different *ALK* fusion variants have been reported in the literature, of which echinoderm microtubule associated protein like 4 (EML4) is the predominant fusion partner (Ou et al, 2012). Published studies in unselected patients with NSCLC report an *ALK* fusion prevalence between 2.7% (Perner et al, 2008; Varella Garcia et al, 2010) and 8% (Kris et al, 2014). The largest study to date in unselected NSCLC patients (Gainor et al, 2013), estimated the prevalence of ALK fusion-positive NSCLC to be 4.4%, in line with the range described above.

Currently, the first generation multi-targeted ALK inhibitor crizotinib, alectinib and LDK378 (ceritinib) and second generation ALK inhibitors are approved by the US FDA for first line treatment of advanced ALK-positive NSCLC. Unfortunately, most patients develop acquired therapeutic resistance to crizotinib, often within the first year of treatment. More potent, second-generation ALK inhibitors (LDK378 (ceritinib), alectinib and brigatinib) are approved after crizotinib failure in this patient population. Several randomized phase III trials have recently completed comparing second-generation inhibitors versus standard of

care in the first-line setting. For example, LDK378 (ceritinib) was recently shown to be superior to standard first-line platinum/pemetrexed chemotherapy (ASCEND-4), and alectinib was found to be superior to crizotinib in two separate studies of crizotinib-naïve, ALK-positive NSCLC patients (J-ALEX and global ALEX; Hida et al, 2017; Peters et al.. 2017). Additional second-generation ALK inhibitors like brigatinib and ensartinib, as well as third-generation inhibitors like lorlatinib, are at various stages of clinical development, with all three currently in randomized phase 3 trials against crizotinib in the first line setting. Of note, crizotinib is known to have limited activity in the central nervous system (CNS), whereas the class of next generation inhibitors has shown robust activity in patients with CNS metastases. Overall, next generation inhibitors, specifically LDK378 (ceritinib) and alectinib are moving into the front-line setting for metastatic ALK-positive NSCLC; however, many patients around the world are still receiving sequential treatment with first-line crizotinib followed by a next-generation ALK inhibitor.

Numerous studies have examined mechanisms of resistance to first and next-generation ALK inhibitors. In patients whose disease has relapsed on crizotinib, approximately 20% have acquired a secondary mutation within the ALK tyrosine kinase domain (Gainor et al. 2016). Over 10 distinct crizotinib-resistant mutations have now been reported. Acquired ALK mutations that have been reported to confer resistance to crizotinib include L1196M, G1202R, S1206Y, G1269A, F1174C and 1151Tins. By contrast, in patients who have relapsed on second-generation ALK inhibitors; close to 50% have acquired a secondary ALK resistance mutation (Gainor et al. 2016). The spectrum of ALK resistance mutations seen with second-generation ALK inhibitors is narrower than that of crizotinib, with ALK G1202R being the predominant resistance mutation emerging after all second-generation ALK inhibitors. As first- and next-generation ALK inhibitors are structurally distinct, their potencies against specific ALK resistance mutations varies widely. For example, alectinib has little activity against ALK I1171 mutations, which are commonly identified in alectinib-resistant tumors; LDK378 (ceritinib) retains potency against I1171 mutations and can effectively overcome these mutations in preclinical and early clinical studies. Numerous other examples of differential activity have been reported, including ALK G1123S (resistant to LDK378 (ceritinib) but sensitive to alectinib) and V1180L (resistant to alectinib but sensitive to LDK378 (ceritinib) (Dong X, et al., 2016).

Most patients who relapse on crizotinib remain sensitive to more potent, next generation ALK inhibitors, suggesting that most crizotinib-resistant tumors remain ALK dependent. Indeed, LDK378 (ceritinib), alectinib and brigatinib are currently approved for crizotinib-resistant patients, without requirement for a biopsy or molecular testing. However, in the setting of relapse on a second-generation ALK inhibitor, preclinical studies using clinical resistant specimens and patient-derived cell lines indicates that about one-half of tumors remain ALK-dependent (typically those tumors harboring ALK resistance mutations), whereas the remaining one-half have become ALK-independent (typically those tumors without ALK resistance mutations)(Gainor et al, 2016). The latter have upregulation of other oncogenic pathways as the primary mechanisms of resistance, or phenotypic changes including epithelial to mesenchymal transition or rarely small cell transformation. Those ALK-dependent tumors may still be sensitive to another ALK inhibitor (if appropriately matched to the ALK mutation), whereas ALK-independent tumors are likely no longer

responsive to another ALK inhibitor. This preclinical work has yet to be validated clinically.

Taken together, these studies suggest that ALK resistance mutations may serve as a critical biomarker to guide selection of subsequent therapy, particularly in the setting of relapse on a second-generation ALK inhibitor. As second-generation ALK inhibitors are already widely used in crizotinib-resistant patients, and are moving rapidly into the first-line setting, there is an urgent need to understand how best to treat patients who have become resistant to a second-generation ALK inhibitor.

2.1 Alectinib

Clinical data in the crizotinib-refractory and crizotinib-naïve settings

Alectinib is FDA-approved for the treatment of patients with ALK+ NSCLC who have progressed on, or are intolerant to, crizotinib and for first-line treatment of ALK+ NSCLC. The initial approval of alectinib was based on two phase 1/2 single-arm studies (NP28673 and NP28761). The global NP28673 alectinib study reported an objective response rate (ORR) of 50.8%, median duration of response of 15.1 months and median progression-free survival (PFS) of 8.9 months (Ou et al., 2016). The North American NP28761 study reported an ORR of 52.2%, median duration of response of 13.5 months and median PFS of 8.1 months (Shaw A, et al., 2016). With longer follow-up, pooled analysis of the two phase 2 studies demonstrated an ORR of 51%, Disease Control Rate (DCR) of 79%, median DOR of 14.9 months, and median PFS of 8.3 months (Yang et al., 2017).

Alectinib has also shown significant CNS activity, with CNS ORR in patients with measurable CNS disease at baseline of 58.8% in NP28673 and 75% in NP28761. CNS duration of response was 11.1 months in both studies.

Alectinib is well tolerated, with the most common AEs (all grades) being constipation (38%); fatigue (32%) and peripheral edema (28%) (Yang JC et al, 2017). Most AEs are grade 1 and grade 2 in severity, with G3-5 AEs occurring in 40% of patients, the most common being dyspnea (4%), blood creatinine phosphokinase increased (4%) and AST and ALT increased (3% each). AEs leading to treatment withdrawal were reported in 6% of patients (n=14).

Two recently reported phase 3 studies, J-ALEX and ALEX, have established alectinib as a new standard of care for newly diagnosed ALK-positive NSCLC patients (Hida, et.al, 2017; . In both studies, crizotinib-naïve patients were randomized to receive either alectinib or crizotinib as first-line therapy. While there were a number of differences in the study designs and study populations, the efficacy results were remarkably similar. Median PFS was approximately 26 months with alectinib in both studies. The hazard ratio for progression was 0.4-0.5 favoring alectinib. Consistent with its known intracranial activity, alectinib was shown to significantly delay time to CNS progression, with a cause-specific hazard ratio of 0.16. Overall, both drugs were reasonably well tolerated, but there were fewer serious adverse events with alectinib in both studies. Approval of first line alectinib was given US regulatory approval in November 2017.

Molecular predictors of response and resistance to alectinib

Recently, the efficacy of alectinib in ALK-positive NSCLC patients with different ALK

point mutations was assessed using pooled data from the two phase 1/2 studies NP28673 and NP28761. All patients received 600mg oral alectinib twice daily. Optional tissue and plasma samples were collected for exploratory ALK mutation analyses using targeted next-generation sequencing methods, including Quintiles Comprehensive Cancer Panel (QCCP) and cancer personalized profiling by deep sequencing (CAPP-Seq) (Newman AM, et al., 2014;.Newman AM, et al., 2016) Tissue analysis was performed using the QCCP assay, which has a sensitivity for single nucleotide variants (SNVs) with an allele frequency ≥5% of 100% and an analytical specificity of >99%. Tissue samples were available at baseline (after crizotinib, before alectinib) for 128 patients. Only two tissue samples were obtained after progression on alectinib for NP28673. Plasma samples were available for all patients at baseline and for 103 patients at progression.

NP28761* **and NP28673*** Pooled Mutation Analysis in Crizotinib-Failed *ALK*-Positive NSCLC: **Baseline *ALK* Mutations**

Table #1

Patient	Dose, mg	Mutation	Sample Type	DOT, Months	PFS, Months	BOR[a]	Disposition at Data Cutoff	Mutation Reported in Literature
[redacted]	600	F1174V	Tissue	19.7	NR	PR	On treatment	Yes
	600	L1196M	Plasma	16.7	NR	PR	On treatment	Yes
	600	S1157F	Tissue	16.6	15.4	SD	Treated beyond progression	No
	600	L1196M	Tissue	14.8	10.0	PR	Treated beyond progression	Yes
	600	R1231W	Tissue	19.5	9.1	PR	Treated beyond progression	No (R>Q)
	600	G1128A	Tissue	8.1	7.9	PR	Withdrew consent	No
	600	V476A	Tissue	5.8	5.5	PR	Discontinued at progression	No
	600	I1171T	Plasma	9.3	5.4	PR	Treated beyond progression	Yes
	760	G1269A	Tissue	4.2	4.2	PR	Discontinued at progression	Yes
	600	C1156F	Tissue	5.9	3.6	PR	Treated beyond progression	No (C>Y)

[redacted]	600	S1206Y	Tissue	3.6	1.4	PD	Deceased at day 120	Yes
	600	F1245C	Tissue	3.6	1.4	PD	Deceased at day 120	Yes
	600	A416P	Tissue	1.1	NR	NE	Deceased at day 35	No
	600	I1171T	Plasma	9.3	5.4	PR	Treated beyond progression	Yes

Data from the mutation analysis using paired tissue and plasma samples from 51 phase 1 and 2 patients were reported at ASCO 2016. Analysis of additional phase 2 plasma samples was also undertaken. cfDNA was isolated from plasma samples from 49 patients who progressed on alectinib, with samples available both pre-alectinib and following progression on alectinib for each cfDNA sample. CAPP-Seq was performed using a custom panel targeting 187 genes for detection of single nucleotide variants (SNVs), insertions/deletions, fusions and copy number variations.

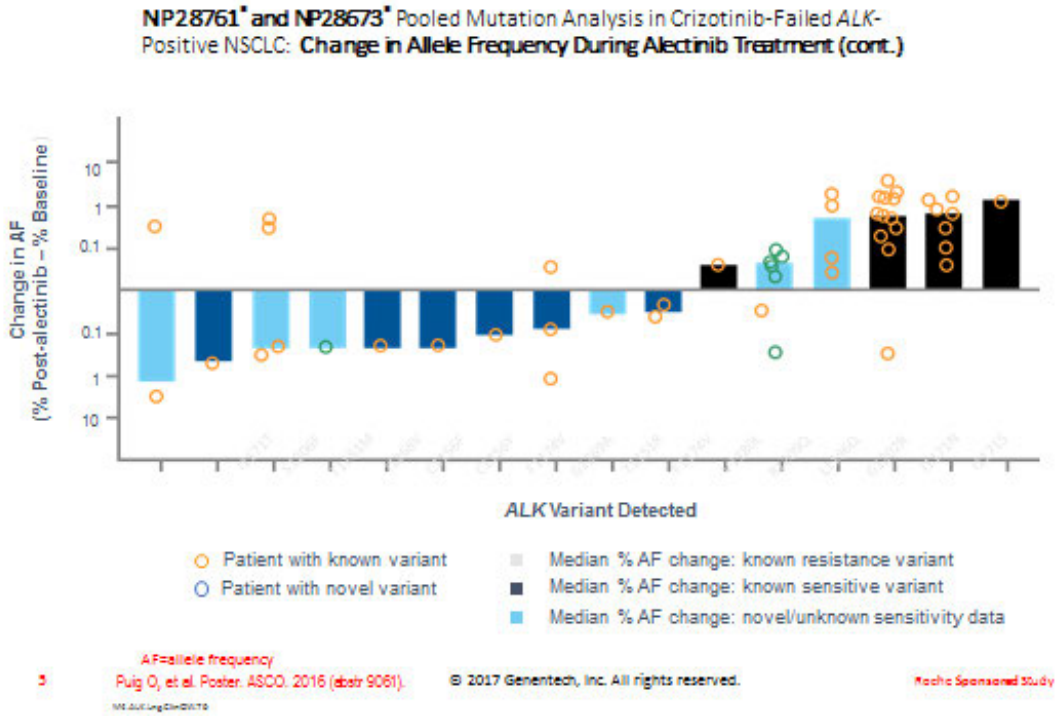
Among the baseline samples, 13 functional ALK mutations were identified in 12 patients (six mutations were previously unreported in the literature; **Table 1)**. PFS of greater than 3 months was seen in patients with baseline F1174V, L1196M, S1157F, R1231W, G1128A, G1269A or C1156F mutations.

At the end of treatment, three new ALK mutations were seen in plasma samples: I1171N, I1171S, and G1202R. All three mutations are known to confer resistance to alectinib.

Table #2: **NP28761*** **and NP28673*** Pooled Mutation Analysis in Crizotinib-Failed *ALK*-Positive NSCLC: **Change in Allele Frequency During Alectinib Treatment**

Variant	Number of Patients With Variant[a]	AF Down During Alectinib Treatment	AF Up During Alectinib Treatment	Response to Alectinib Reported in Literature
T1151M	3	2	1	Resistance/sensitivity
T1151R	1	1	0	Unknown
C1156F	1	1	0	Sensitivity
C1156Y	1	1	0	Sensitivity
F1174L	2	2	0	Sensitivity
F1174V	1	1	0	Sensitivity
S1206F	1	1	0	Sensitivity
I1268V	1	1	0	Novel
G1269A	1	1	0	Sensitivity
I1171T	2	1	1	Resistance/sensitivity
I1171N	7	0	7	Resistance
I1171S	1	0	1	Resistance
V1180L	1	0	1	Resistance
L1196Q	4	0	4	Unknown
G1202R	12	1	11	Resistance
R1209Q	6	1	5	Novel

Figure #1: NP28761* and NP28673* Pooled Mutation Analysis in Crizotinib-Failed *ALK*-Positive NSCLC: Change in Allele Frequency During Alectinib Treatment (cont.)



Several known resistance mutations increased in frequency in plasma samples following alectinib treatment in one patient: APCG871V, EML4-ALK, ALK G1202R C>T and C>G.

The convergent evolution of two different sub-clones of G1202R suggests strong selective pressure to develop the G1202R mutation in response to alectinib. In contrast, ALK I1171T, KCNN3-ALK and ALKC1156F decreased after alectinib treatment.

Analysis of ALK mutations in response to alectinib using plasma samples from the additional phase 2 plasma samples revealed 47 missense SNVs in 21 different patients. The change in allele frequency (AF) while on alectinib generally matched the expected pattern. SNVs known to be resistant to alectinib (e.g. G1202R, I1171N/S) increased in AF during treatment, while those known to be sensitive to alectinib (e.g. F1174V, G1269A) decreased in AF during treatment **(Table 2 and Figure 1)**.

In the additional phase 2 samples, R1209Q, a variant in the ALK catalytic domain, was detected in six patients; in five of these patients, the variant was only detected after progression on alectinib, suggesting it may be a novel resistance mechanism. Patient [redacted] was the only patient with an R1209Q mutation that showed a reduction in AF during alectinib treatment; however, known resistance variants (G1202R and I1171N) increased in AF, suggesting that a different subclone showed stronger resistance to alectinib.

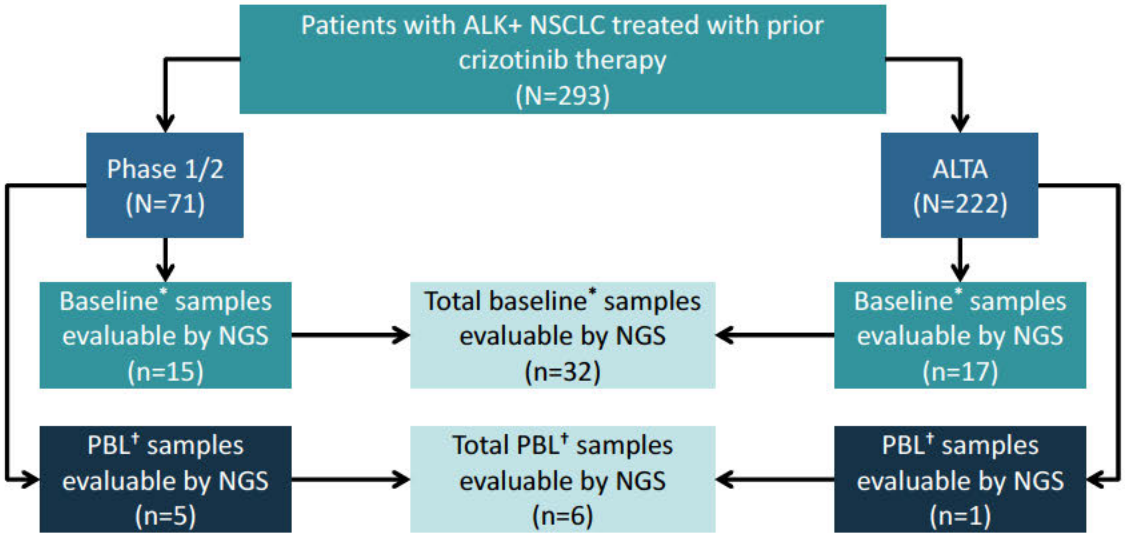
Taken together, these data demonstrate that alectinib is clinically active against native ALK and several ALK variants that can cause resistance to crizotinib. Resistance mutations including I1171S/N, G1202R and the novel R1209Q may occur during treatment with alectinib. These analyses also show that in the absence of tissue samples, assessing tumor DNA in plasma samples may be an alternative non-invasive way to monitor for the appearance of resistance mutations during therapy, some of which may be targetable by other ALK inhibitors.

2.2 Brigatinib (20-JAN-2022)

Clinical data

Brigatinib is FDA-approved for patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib and for first-line use. The relationship between ALK mutation status and efficacy of brigatinib has been evaluated in two ongoing studies: a first-in-human phase 1/2 study (AP26113-11-101), which assessed a variety of dose levels (30 mg to 300 mg daily), and a phase 2 study ("ALTA"; AP26113-13-201) (Gettinger, 2016). In the ALTA study, patients with ALK+ NSCLC who had progressed on crizotinib, were randomized to one of two regimens of brigatinib: 90 mg QD and 180 mg QD with 7-day lead-in at 90 mg QD (90 mg QD → 180 mg QD). These studies included 71 and 222 patients, respectively, with ALK+ NSCLC and prior treatment with crizotinib. As shown in Figure 2, tumor tissue samples collected after crizotinib therapy (baseline; n=32 total) were used to assess the efficacy of brigatinib according to baseline mutation status. Tumor tissue samples collected after disease progression on brigatinib (post-baseline; n=6 total) were used to identify potential mechanisms of resistance to brigatinib. All samples were analyzed using the FoundationOne®CDx next generation sequencing (NGS) platform to assess the presence of secondary mutations in ALK kinase domain (KD) (as well as the presence of *ALK* rearrangements) or mutations in other genes.

Figure #2: Patient Flow Chart: Mutational Analysis of Patients from Phase 1/2 and ALTA trials



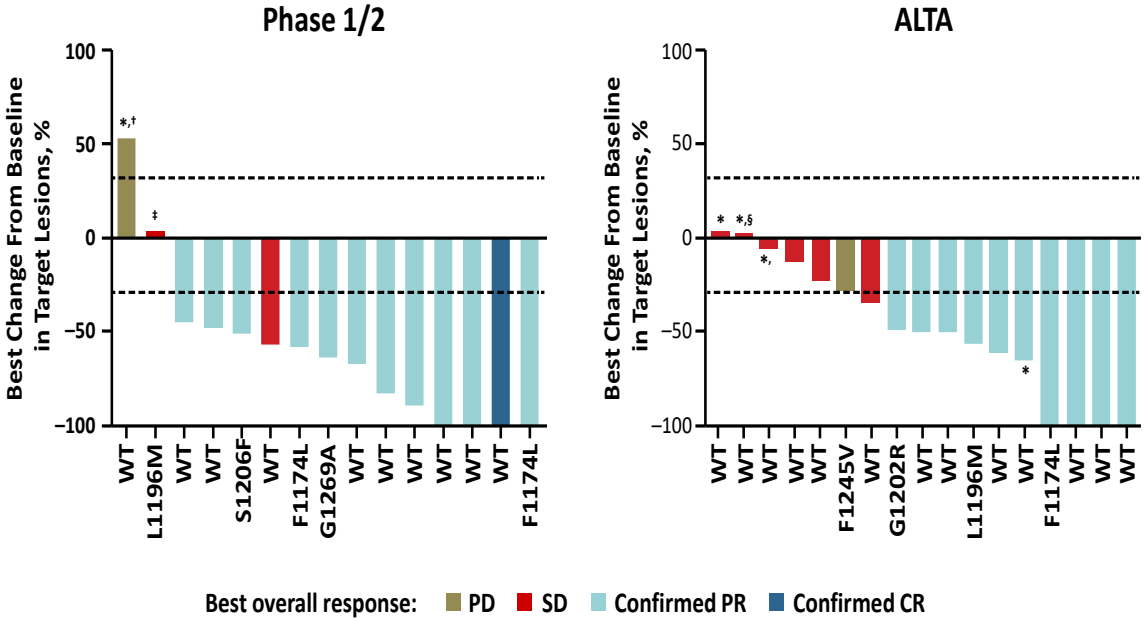
*Baseline samples were collected after progression on crizotinib treatment and before brigatinib treatment. †Optional PBL samples were collected after progression on brigatinib treatment.
NGS=next-generation sequencing; PBL=post-baseline.

Analysis of Baseline Samples

In the phase 1/2 study, evaluable baseline tumor samples were provided by 15 patients. ALK rearrangements were detected in 14/15 patients and secondary mutations in the ALK KD in 5 of those 15 patients. Of the 14 patients with *ALK* rearrangements, responses were observed in patients without and with secondary ALK KD mutations. All 9 patients without secondary ALK KD mutations had a response (8 PR, 1 CR, with 8 responses confirmed) and 4/5 patients with secondary mutations had a response (4 PR, all were confirmed responses). Responses were observed in patients with S1206F (n=1), F1174L (n=2), and G1269A (n=1) mutations at baseline. A patient with L1196M, who received brigatinib for only 29 days, had the tumor scan taken 32 days after the last dose, had a best response of SD. All 5 patients with secondary mutations were treated with a 180 mg QD regimen (with or without the 7 day lead-in at 90 mg QD). These results are summarized in the form of a waterfall plot in Figure 3 and swimmer's plot in Figure 4.

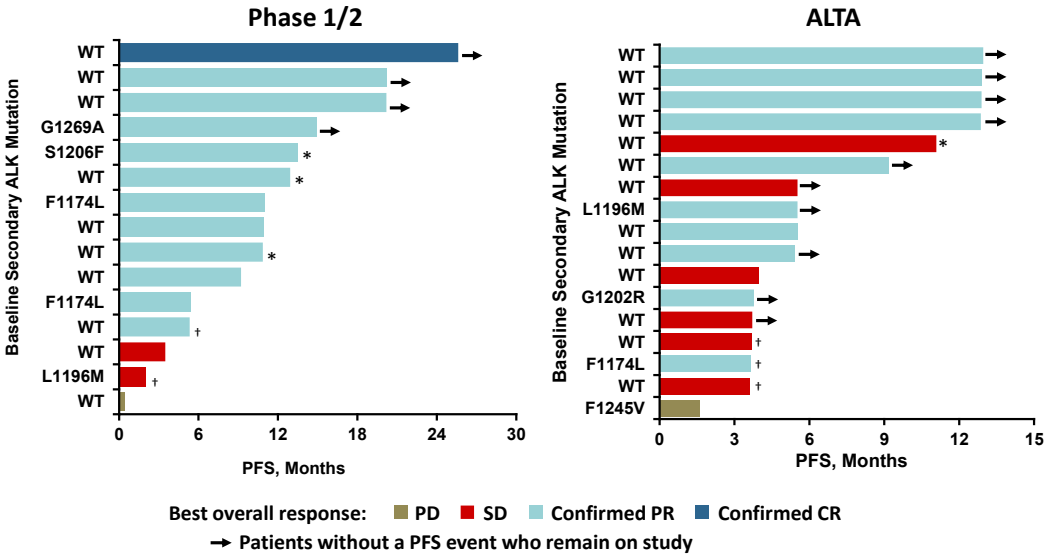
In the ALTA study, evaluable baseline tumor samples were provided by 17 patients. *ALK* rearrangements were detected in 13/17 patients and secondary mutations in the ALK kinase domain in 4/17 patients. Of the 13 patients with *ALK* rearrangements, responses were observed in patients without and with secondary ALK kinase domain mutations: 6/9 patients without ALK KD mutations had a response and 3/4 patients with ALK KD mutations had a response (all 9 responses were confirmed PRs). Responses were observed in patients with G1202R (n=1; 90 mg QD → 180 mg QD), L1196M (n=1; 90 mg QD → 180 mg QD), and F1174L (n=1; 90 mg QD) mutations at baseline. A patient with F1245V (90 mg QD) had a best response of PD. These results are summarized in Figure 3 and Figure 4; additional details can be found in Section 3.2.

Figure #3: Confirmed Responses Observed in Patients with and without ALK Mutations at Baseline



*ALK fusion negative by NGS at baseline. †PIK3CA E545K mutation, §EGFR amplification, ||BRAF G596R mutation detected at baseline. ‡Patient receiving brigatinib for 29 days; tumor scan taken 32 days after last dose.

Figure #4: Durable Responses Observed in Patients with and without ALK Mutations at Baseline



*Patients with a PFS event who remain on study.
†Patients who discontinued treatment or were otherwise censored before PFS event.

Analysis of Post-Baseline Samples

Evaluable post-baseline samples have been analyzed from 5 patients in the phase 1/2 study and 1 patient in the ALTA study. Table 4 shows a summary of the results of the post-baseline mutation analysis (red box), along with additional details regarding patient treatment and outcome that assist in interpretation of the results, such as the brigatinib dosing regimen, time to progression, time to post-baseline biopsy, and time to brigatinib discontinuation. All 6 patients achieved a confirmed response on brigatinib. Note that baseline biopsies were only available from 2 of these 6 patients.

Table #4: Summary of Post-Baseline Mutation Analysis of Brigatinib Treated Patients

Patient ID	BL secondary ALK KD mutation status (% of reads)	Brigatinib Regimen (mg)	Best Confirmed Response	Time to Progression (days)	Time to PBL biopsy# (days)	Time to Brigatinib D/C (days)	PBL secondary ALK KD mutation status (% of reads)	Comment
[redacted]	No tissue	120 QD	PR	165	394	609	None	Possible emergence of ALK-independent resistance
	F1174L (18%)	180 QD[c]	PR	335	344	487	F1174L (5%)	Possible emergence of ALK-independent resistance
	No tissue	180 QD[c]	PR	165	261	258	I1171H (11%) D1203N (8%) G1269A (6%)	Possible compound mutation in ALK kinase domain
	No tissue	90 QD	PR	225	267	277	F1174L (54%) E1210K (27%)	Possible compound mutation in ALK kinase domain
	WT	90 QD	PR	331	575	616	G1202R (14%)	PBL sample collected 9.7months after brigatinib dose escalation to 120 mg BID
	No tissue	60 BID	PR	867	964	Ongoing	G1202R (4%)	BRAF G469A mutation (2%) also detected in PBL sample Lesion regression following brigatinib dose escalation to 240mg QD

*ALTA patient; D/C: discontinuation; # All PBL samples collected while on, or within 3 days of discontinuation of brigatinib therapy

[a]All PBL samples collected while on or within 3 days of D/C of brigatinib therapy; [b]ALTA patient
[c]180 mg QD with 7 day lead-in at 90 mg QD; KD=kinase domain; D/C=discontinuation; BL=baseline; PBL=post-baseline

In the first two patients (patient IDs [redacted], no new ALK mutations were detected at progression, suggesting the possible emergence of an ALK-independent mechanism of resistance in these patients. Note that patient [redacted] had F1174L detected at baseline (18%), achieved a confirmed PR, and after progression on brigatinib had F1174L detected after 11.3 months of treatment, though at a lower level (5%). In the absence of the baseline sample one could have concluded, erroneously, that this provided evidence that F1174L is a resistance mutation for brigatinib. This is clearly not the case since, as noted above, 3/3 patients with an F1174L mutation at baseline achieved confirmed responses on brigatinib.

In the next 2 patients (patient IDs [redacted], multiple ALK mutations were detected at progression, suggesting the possible emergence of compound mutations, that is 2 (or more) mutations in the same ALK allele. Since baseline tumor samples were not provided it cannot be determined whether any of the single mutants, or the compound mutants themselves, developed on brigatinib treatment or were pre-existing. Both patients had a

confirmed PR but progressed after 5.4 and 7.4 months of treatment.

In the last 2 patients, a G1202R mutation was detected at progression. In patient [redacted] no ALK mutation was detected at baseline, indicating that G1202R emerged during brigatinib treatment. This patient achieved a confirmed PR at the initial dose of 90 mg QD, and then escalated to 120 mg BID upon progression after ~11 months of treatment. G1202R was subsequently detected in a tumor biopsy collected after 18.9 months of treatment. Since there were no intervening biopsies, the kinetics with which G1202R emerged, and whether or not dose escalation had an effect on those kinetics, is not known.

Finally, in patient [redacted] G1202R was detected in a biopsy collected nearly 32 months after the start of brigatinib treatment. This patient achieved a confirmed PR at the initial dose of 60 mg BID that was maintained until month 28.5. Upon detection of a G1202R mutation in a biopsy collected at month ~32, the brigatinib dose was escalated to 240 mg QD. Regression of the lesion was observed upon dose escalation.

In summary, by a variety of assessments that relate exposure levels achieved in patients to inhibitory concentrations required in cellular assays, 180 mg QD brigatinib is predicted to lead to levels of exposure sufficient to inhibit native ALK and all single resistance mutants, consistent with the profile of brigatinib as a pan-ALK mutant inhibitor. These include mutants associated with preclinical and/or clinical resistance to LDK378 (ceritinib) (such as L1152R/P, L1198F, and F1174C/L/V) and alectinib (such as T1151ins, I1171N, and V1180L). Importantly, there is limited data suggesting activity of brigatinib against G1202R. However, in this case, preclinical results suggest that optimal efficacy of brigatinib against G1202R may be dose-dependent.

The presence of compound ALK mutations, or ALK independent mechanisms, appears to be associated with brigatinib resistance. In addition, G1202R was clearly acquired during brigatinib treatment in one patient. However it was detected in a biopsy collected nearly 19 months after treatment initiation and for the first 10 months the patient was dosed with 90 mg, not at the currently recommended dose of 180 mg. G1202R was also detected in another patient after a long duration of brigatinib treatment (31.7 months) and direct evidence that a higher than standard dose of brigatinib could induce tumor regression was obtained in that patient.

2.3 LDK378 (Ceritinib)

LDK378 (ceritinib) was the first of the second-generation ALK inhibitors to be granted FDA approval for the treatment of advanced, crizotinib-pretreated ALK+ NSCLC. LDK378 (ceritinib) is approximately 20 times more potent than crizotinib in vitro and inhibits the most common ALK resistance mutations, including L1196M and G1269A. In the phase 1 study (ASCEND-1), LDK378 (ceritinib) achieved durable systemic and intracranial responses in both crizotinib-naïve and crizotinib-pretreated patients (Kim, 2016). The median PFS with crizotinib was 18.4 months and 6.9 months in crizotinib-naïve and crizotinib-pretreated patients, respectively.

To understand genetic determinants of response to LDK378 (ceritinib), tumor biopsies from

patients treated with LDK378 (ceritinib) in ASCEND-1 were analyzed by next generation sequencing using the Foundation Medicine platform which targeted 295 genes. A total of 146 patients who had enrolled in ASCEND-1 and received at least 1 dose of LDK378 (ceritinib) had biopsies submitted to Foundation Medicine. NGS data were successfully generated for 85 patients with baseline biopsies (crizotinib-naïve n=31, crizotinib pretreated n=54).

Among the 85 patients, 25 had received prior crizotinib and were confirmed as harboring an ALK rearrangement. Of these 25, 9 (36%) had ALK mutations detected in the baseline biopsy sample, while the remaining 16 (64%) did not. All 9 patients had mutations within the ALK TK domain, and benefitted from LDK378 (ceritinib) treatment, except for one with a G1202R mutation (Table 4 below). LDK378 (ceritinib) was effective in two patients carrying a C1156Y mutation. One patient harboring concomitant I1171T and F1174V mutations benefitted from LDK378 (ceritinib) treatment. The ALK E1129V mutation, which has never been reported in NSCLC but has been reported to confer resistance to crizotinib in NPM-ALK expressing BaF3 cells, was also sensitive to LDK378 (ceritinib) treatment. Finally, one patient had a novel ALK T1151R mutation (not previously reported and not shown in the table) and was sensitive to LDK378 (ceritinib).

Table 5: LDK378 (ceritinib) efficacy in patients with ALK mutations in biopsies collected after (or close to) last day of prior ALKi treatment*

Patient	ALK mutation(s)	BOR	PFS, days	Event	Prior ALKi
1	E1129V	PR	337	PD/death	Crizotinib
2	L1196M	PR	267	PD/death	Crizotinib
3	I1171T, F1174V	PR	250	PD/death	Crizotinib + alectinib
4+	C1156Y	SD	246+	Ongoing without an event	Crizotinib
5	L1196M	PR	213	PD/death	Crizotinib
6++	C1156Y	PR	174	PD/death	Crizotinib
7	L1196M	PR	163	PD/death	Crizotinib
8	G1202R	Unknown	26	PD/death	Crizotinib + alectinib

*Efficacy per blinded independent review committee
+ Biopsy 5 days before end of crizotinib treatment; +patient ongoing without an event
++ Biopsy on last day of crizotinib treatment
BOR, best overall response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

For 2 patients in ASCEND-1, baseline and post LDK378 (ceritinib) biopsies were available. One patient who received LDK378 (ceritinib) as his first ALK TKI developed *MET* amplification at the time of progression. The second patient had a *JAK2* amplification and a *CDKN2A/B* deletion in the post LDK378 (ceritinib) biopsy (and not in the baseline sample). Thus, in both cases, patients likely developed off-target mechanisms of acquired resistance.

2.4 Crizotinib

Crizotinib has received traditional or conditional approval for the treatment of patients with advanced ALK-positive NSCLC in many countries, including the United States (US), Europe (EU), and Japan. Crizotinib has also received traditional approval for the treatment of patients with advanced ROS1-positive NSCLC in the US.

Crizotinib is a selective ATP-competitive small-molecule inhibitor of ALK, ROS1, and c-MET/Hepatocyte Growth Factor Receptor (HGFR) tyrosine kinases and their oncogenic variants (eg, ALK or ROS1 fusion proteins or c-MET/HGFR mutant variants). Consistent with this mechanism of action, crizotinib inhibited phosphorylation of c-MET/HGFR and selected ALK fusion or mutant variants in tumor cells both in vitro and in vivo, and ROS1 in vitro. Crizotinib exhibited potent and selective growth inhibitory activity against tumor cells exhibiting translocation/inversion or selected mutations involving the ALK gene locus (EML4-ALK or nucleophosmin [NPM]-ALK fusion variants).

Oral dosing of crizotinib 250 mg twice daily (BID) showed plasma concentrations reach steady state within 15 days and remain stable. The mean apparent terminal half-life was 42 hours in cancer patients after a single dose. Crizotinib is absorbed with a peak plasma concentration occurring between 4 and 6 hours under fasting conditions. Crizotinib is a substrate of P- glycoprotein and is predominately metabolized by CYP3A4/5. Elimination of crizotinib was related to its hepatic, and possibly gastrointestinal, metabolism with a mean of 63.1% of [14C] crizotinib excreted in the feces and 22.2% in the urine (crizotinib Investigator's Brochure [IB]).

Overall, the adverse events (AEs) reported for crizotinib in clinical studies were considered generally tolerable and manageable. For single-agent crizotinib, the most common AEs (≥20% of patients) reported as of March 2015 from 1761 (95.7%) of the 1840 patients with advanced NSCLC as treatment-related were vision disorders (60.4%), nausea (49.1%), diarrhea (48.1%), vomiting (43.9%), edema (38.1%), constipation (32.4%), elevated transaminases (30.4%), fatigue (21%), and neutropenia (20.4%). The majority of AEs were Grades 1 or 2 in severity, while treatment-related AEs of Grades 3, 4, or 5 in severity were observed among 701 (38.1%) advanced NSCLC patients who received at least 1 dose of single-agent crizotinib 250 mg BID. The most common (≥ 2%) Grade 3 treatment-related AEs were neutropenia, elevated transaminases, hypophosphatemia, lymphopenia, leukopenia, and fatigue. The most common (≥ 1%) Grade 4 treatment-related AEs were neutropenia, and elevated transaminases. The Grade 5 treatment-related AEs were interstitial lung disease (ILD) (0.4%), death (0.2%), and pneumonia, hepatotoxicity, lung infection, disseminated intravascular coagulation, arrhythmia, dyspnea, pulmonary embolism and deep vein thrombosis (0.1% each) (crizotinib IB).

Clinical trials of crizotinib in both the first- and second-line ALK-positive NSCLC settings showed high rates of objective tumor response, and the responses were rapid and durable (PROFILE 1007 and PROFILE 1014). However, essentially all patients relapse on crizotinib, many within the first year of treatment. To date, numerous mechanisms of crizotinib resistance have been reported. While most crizotinib-resistant tumors remain ALK-dependent, only 20-30% of resistant tumors acquire a secondary ALK resistance mutation.

Numerous crizotinib-resistant mutations have now been reported, including ALK L1196M (the gatekeeper mutation), G1269A, I1151Tins, L1152R, C1156Y, I1171T/N/S, F1174C/L/V, V1180L, G1202R, S1206Y, and E1210K, among others. More potent second- and third-generation ALK inhibitors can overcome many of these mutations.

While alectinib has become the new standard of care for newly diagnosed patients with advanced ALK+ NSCLC (Peters et al., NEJM 2017), crizotinib may still play an important role in specific settings. First, as noted above, crizotinib is a potent MET inhibitor. Second and third generation ALK inhibitors (with the exception of ensartinib) do not inhibit MET, and indeed, MET amplification has been shown to function as a bypass mechanism mediating resistance to next generation inhibitors such as alectinib. In one case report, a patient who had developed resistance to alectinib due to MET amplification responded to crizotinib (Gouji et al., JTO 2014), validating the role of MET in driving resistance.

Crizotinib may also play a role in patients who have received sequential ALK inhibitors and have developed compound (i.e., double) ALK mutations including ALK L1198F. This was first demonstrated in a case report of a patient who had been treated with crizotinib, LDK378 (ceritinib) and lorlatinib (Shaw et al., NEJM 2016). This patient developed the ALK C1156Y resistance mutation after failing on crizotinib. She did not respond to LDK378 (ceritinib), but did respond durably to lorlatinib. However, when she relapsed on lorlatinib, her tumor had acquired the compound ALK C1156Y/L1198F mutation. In vitro studies showed that this L1198F compound mutation conferred resistance to lorlatinib and other next generation ALK inhibitors, but unexpectedly conferred sensitivity to the less potent ALK inhibitor crizotinib. Indeed, the patient was treated with crizotinib and experienced a dramatic and durable response. Additional in vitro studies have demonstrated that ALK L1198F can resensitize other crizotinib-resistance mutations including ALK L1196M and even ALK G1202R (Shaw et al., NEJM 2016). Thus, crizotinib may be an effective therapeutic option for patients when their resistance is due to an ALK L1198F-containing compound mutation.

2.5 Ensartinib (X-396) (17-FEB-2020)

Ensartinib is a potent, novel and specific ALK inhibitor. In biochemical assays, ensartinib was tested against ALK and all alterations available in the Reaction Biology panel (Reaction Biology Corp.). It showed potent inhibition of all of them with IC50 <4 nM. The wild-type, and F1174, C1156Y, L1196M, S1206R, and T1151 mutants are particularly sensitive to ensartinib with IC50 of <0.4 nM, while the G1202R mutant is least sensitive (IC50 = 3.8 nM). Besides ALK, ensartinib also potently inhibits TRKA fusions, TRKC, and ROS1. Kinases inhibited at higher concentrations are EphA2, EphA1, EphB1 and c-MET. Compared to crizotinib, ensartinib was approximately 10-fold more potent in *in vitro* assays (Lovly et al. 2011). It is particularly potent against the L1198F mutant, which is resistant to lorlatinib (1.1 nM for ensartinib vs. 26.7 nM for crizotinib) (Lovly, unpublished data).

In pre-clinical studies, ensartinib exhibited a favorable efficacy profile, including anti-tumor activity against multiple ALK variants including those that are resistant to crizotinib. Data from animal studies support the potential utility of ensartinib in crizotinib-resistant tumors and the potential use of ensartinib for the treatment of NSCLC tumors that have metastasized to the brain.

Clinical Efficacy in ALK+ NSCLC Patients
There is an ongoing Phase 1/2 study with ensartinib (NCT01625234). In this trial, responses have been observed in patients with ALK-positive NSCLC, including patients who are crizotinib-naïve, patients who have received prior crizotinib, and in patients with CNS metastases. In addition, the drug has generally been well tolerated.

As of Feb. 15, 2017, 97 patients have been enrolled in the ongoing Phase I/II study, with 60 ALK+ efficacy evaluable patients dosed at ≥200mg once daily. To be evaluable for efficacy, patients must have completed at least 1 cycle of treatment (each cycle is approximately 28 days) and had a post baseline response assessment. Among the 15 patients who didn't receive a prior ALK TKI, 12 achieved a partial response (PR), a response rate (RR) of 87%. Two patients who did not respond were ALK negative via plasma next generation sequencing (NGS). Among the 29 patients who received prior crizotinib but no other ALK TKI, 20 had a PR (RR: 69%), 8 had stable disease (SD), and 1 had progressive disease (PD) as best response, yielding an overall disease control rate (DCR) of 97%. Four of the 16 patients who received multiple ALK TKIs had a PR, and another 4 had SD, a DCR of 50%. Fourteen patients (3 were ALK TKI naïve, 8 had prior crizotinib only, 3 had multiple ALK TKIs) had CNS target lesions at baseline. Of these 14 patients, 2 had a complete intracranial response (CR), 7 achieved a PR, and 4 had SD, a 64% RR and a DCR of 93% (Horn 2018).

The overall median PFS for ALK-positive evaluable patients was 9.2 months. In the ALK TKI naive patients, the median PFS was 26.2 months. Of the patients with prior crizotinib only, the median PFS was 9.0 months. Within the subgroup that received prior crizotinib and a second-generation ALK TKI, the median PFS was 1.9 months (Horn et al. In Press).

NGS was performed by Resolution Bioscience on ctDNA from plasma samples on some patients who had prior ALK TKI(s), and various responses were observed as summarized below (Table 6). NGS panel targeted actionable mutations and rearrangements found in NSCLC.

Table 6: Activity Seen in Patients with ALK Kinase Domain Mutations

ALK Resistant Mutation	Best Response	Prior ALK TKI	Dose (mg)	PFS* (mo)	DOR* (mo)	%CFB* Best Response
L1196M	PR	crizotinib	225	5.6	3.7	-47.4
L1196M, G1269A	PR	crizotinib	225	7.4	5.6	-53.7
T1151M	PR	crizotinib	250	3.7	1.9	-48.5
G1202R	PR	crizotinib and LDK378 (ceritinib)	225	5.7	3.9	-36.4
L1152V, G1269A	PR	crizotinib and alectinib	225	3.6	1.9	-91.4
F1174V	PR	crizotinib	225	15.5	12	-40

S1206F	SD	crizotinib	225	2.6	-	0
E1154K	SD	crizotinib	225	5.7	-	-26.8
G1202R	PD	crizotinib and LDK378 (ceritinib)	225	1.8	-	13.2
D1203N, C1156Y	PD	crizotinib and LDK378 (ceritinib)	225	1.7	-	39.2

* PFS (progression free survival); DOR (duration of response); CFB (change from baseline)

2.6 Lorlatinib

Preclinical Data

Lorlatinib (PF-06463922) is a selective, ATP competitive small molecule inhibitor of ALK and c-ROS oncogene 1 (ROS1) receptor tyrosine kinases that was specifically designed to address mechanisms of resistance. In preclinical studies, lorlatinib demonstrated potent and selective inhibitory activity against wild-type ALK, most known acquired crizotinib-resistant ALK mutations (Johnson et al, 2014; Zou et al, 2015; Toyokawa 2014). Lorlatinib was also capable of penetrating the blood-brain barrier (BBB) in preclinical animal models (Johnson et al, 2014; Zou et al, 2015).

In vitro, lorlatinib potently inhibited catalytic activities of wild-type ALK and 15 different ALK mutant kinases in recombinant enzyme and cell-based assays (Ki or 50% inhibitive concentration [IC50] ranged from <0.07 nM to 113 nM) (Zou et al, 2015; Gainor et al, 2016). The 15 ALK mutants analyzed included crizotinib-resistant mutations 1151Tins, L1152R, C1156Y, L1196M, G1202R, S1206Y, E1210K, and G1269A; LDK378 (ceritinib)-resistant mutations F1174L, F1174C, G1202del, and D1203N; as well as the alectinib-resistant I1171T/N/S mutations. Among these mutations, 1151Tins and G1202R confer high levels of resistance to almost all of the second generation ALK inhibitors tested, including LDK378 (ceritinib) and alectinib (Shaw & Engelman, 2013; Friboulet et al, 2014; Ou et al, 2014; Gainor et al, 2016). In instances of LDK378 (ceritinib) resistance, it was reported that 5 of 11 patients (46%) whose tumors developed resistance to therapy acquired ALK mutations of either G1202R or F1174L, and that C1156Y and L1152R ALK mutants conferred resistance to LDK378 (ceritinib) (Friboulet et al, 2014). For alectinib resistance, in addition to G1202R, mutations at amino acid position I1171 have been reported to be the most common (Ou et al, 2015; Gainor et al, 2016).

Lorlatinib also showed potent growth inhibitory activity and induced apoptosis in human H3122 NSCLC and Ba/F3 pro B cells engineered to express various ALK mutants (IC50 = 2.4 nM to 80 nM). Compared with crizotinib and the second generation ALK inhibitors, LDK378 (ceritinib), alectinib, and lorlatinib showed significantly improved inhibitory activity against wild type or mutant forms of ALK (Zou et al, 2015). In H3122 human NSCLC cells harboring an endogenous EML4-ALK V1 (E13:A20) fusion proteins, lorlatinib was >10-fold more potent than crizotinib, LDK378 (ceritinib), and alectinib at inhibiting both the ALK kinase activity and cell growth. In a panel of Ba/F3 cell lines engineered to express various mutant forms of ALK fusion, lorlatinib inhibited cell proliferation mediated by EML4-ALK^{F1174L} and EML4-ALK^{S1206Y} at IC_{50} values >4-fold more potent than that of

crizotinib, LDK378 (ceritinib) or alectinib, and it was ≥3-fold more potent than crizotinib, LDK378 (ceritinib) or alectinib against EML4-ALK C1156Y, EML4-ALK 1151Tins or EML4-ALK G1202R driven Ba/F3 cell growth (Zou et al, 2015).

In vivo, lorlatinib demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express EML4-ALK, EML4-ALK L1196M, EML4-ALK G1269A, EML4-ALK G1202R, EML4-ALK I1171T, or NPM-ALK at low nanomolar free plasma concentrations. These effects were associated with significant decreases in cellular Ki67 expression and increased cleaved-caspase3 levels in tumors. In addition, lorlatinib achieved brain exposure of 20-30% of plasma levels in mice and rats. In mice bearing orthotopic EML4-ALK or EML4-ALK L1196M positive brain tumor implants, lorlatinib caused tumor shrinkage and prolonged survival (Zou et al, 2015). The overall anti-tumor efficacy of lorlatinib was dose dependent and strongly correlated with inhibition of ALK phosphorylation and downstream signal transduction.

Lorlatinib Clinical Evidence

The First in Patient (FIP) single-agent dose escalation and expansion study (Study B7461001) began on 23 January 2014. This Phase 1/2 study is enrolling patients with advanced ALK-positive NSCLC and patients with advanced ROS1-positive NSCLC, with or without asymptomatic CNS (central nervous system) metastases.

As of the data cutoff of 15 January 2016, lorlatinib has been administered to 54 patients in the Phase 1 part of this study across 7 QD doses of 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg and 3 twice a day (BID) doses of 35 mg BID, 75 mg BID, and 100 mg BID. Of the 3 patients enrolled in the 200 mg QD cohort, 1 dose-limiting toxicity (DLT) occurred in a patient who failed to receive 16 of the planned 21 doses of lorlatinib due to Grade 1 and Grade 2 central nervous system adverse events (AEs). A decision was made among the Sponsor and investigators to re-test lower doses to better understand and evaluate the CNS effects observed at the higher dose levels. Lower doses of 50 mg QD, 75 mg QD, and 100 mg QD were evaluated and BID regimens tested were 35 mg BID, 75 mg BID, and 100 mg BID. A food effect cohort was tested at 100 mg QD (planned as 6 patients).

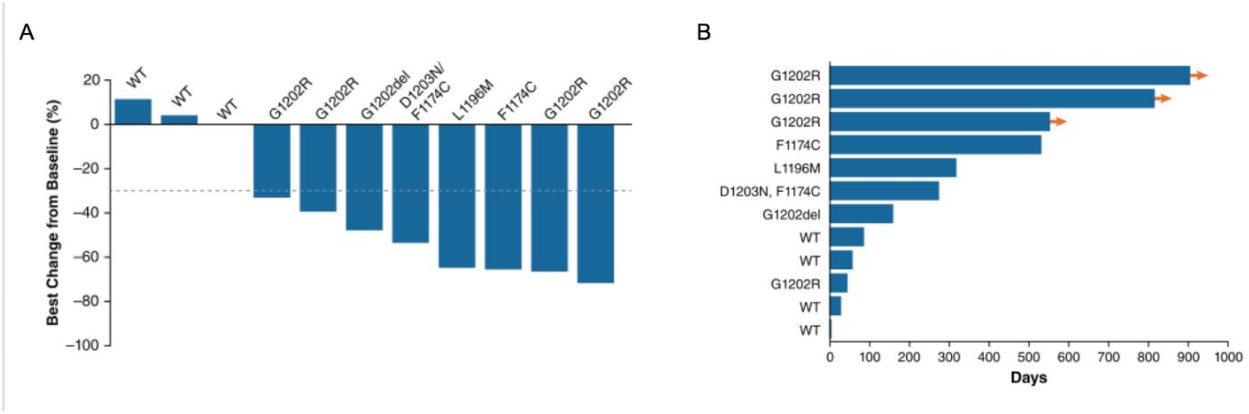
Additionally, based on the PK data observed, simulated patient exposure suggested that the100-mg QD dose was the lowest dose that would exceed the lorlatinib efficacious concentration (Ceff) of 150 ng/mL during the majority of the dosing interval once steady state was reached. The Ceff of 150 ng/mL was a plasma concentration predicted to result in >80% tumor growth inhibition of the ALK G1202R resistance mutation. Further, lorlatinib demonstrated durable clinical activity at 100-mg QD dose, which indicated that this compound has anti-tumor activity both intra- and extracranially. The 100-mg QD dose was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

In the phase 1 study, lorlatinib has demonstrated a confirmed ORR of 46% among ALK-positive patients treated with two or more ALK inhibitors. Median duration of response was 11.7 months, and median PFS among the 26 ALK-positive patients treated with 2 or more ALK TKIs was 9.2 months. In addition, lorlatinib demonstrated marked intracranial activity,

with durable responses noted in ALK-positive patients who had failed multiple ALK TKIs, including LDK378 (ceritinib) and alectinib (Shaw et al., 2017).

Of note, early in the phase 1 study, lorlatinib was noted to be active in patients harboring G1202R-positive tumors who had failed prior LDK378 (ceritinib), alectinib, and brigatinib. To examine molecular correlates of response to lorlatinib in ALK-positive patients who had failed 2 or more ALK TKIs, Pfizer analyzed 12 patients who had undergone a biopsy on the last TKI received. Eight of the 12 samples were found to harbor known ALK resistance mutations. In the remaining 4 cases, no genetic mutation in ALK was detected. As shown in **Figure 5A** (below), tumor regression was observed in all patients with lung cancers harboring ALK resistance mutations, including 5 tumors with ALK G1202R or G1202del. In patients without detectable ALK resistance mutations, none demonstrated tumor regression. Consistent with this data, the duration of treatment with lorlatinib was longer in those patients with ALK resistance mutations compared to those without (mean 448 vs 42 days, respectively, p=0.027; Figure 5B).

Figure 5A-B. Response to Lorlatinib and Correlation with ALK Resistance Mutations in Patients Treated with ≥2 ALK TKI. (A) Best systemic response. (B) Duration of treatment



Resistance to lorlatinib

In a brief report, Shaw et al (2016) described a patient with crizotinib resistance due to the ALK C1156Y mutation who subsequently responded to lorlatinib. When the tumor relapsed, sequencing of the resistant tumor revealed an ALK L1198F mutation in addition to the C1156Y mutation. The L1198F substitution confers resistance to lorlatinib through steric interference with drug binding. However, L1198F paradoxically enhances binding to crizotinib, negating the effect of C1156Y and resensitizing resistant cancers to crizotinib. The patient received crizotinib again, and she achieved a durable (~6 month) response.

2.7 Summary of NRG-LU003 (17-FEB-2020)

The NCI-NRG-ALK Protocol proposes to study ALK positive non-squamous NSCLC patients who develop progression on a second-generation ALK inhibitor, and to establish a treatment algorithm for these patients based on resistance mechanisms identified by tissue biopsies. The patients may have received the second-generation ALK inhibitor as first- or second-line therapy. Initially, patients will undergo tissue biopsy (if they do not have residual

tissue available from a biopsy obtained within the last 3 months) along with blood sampling for cfDNA analysis. The sensitivity of circulating-free (cf) DNA testing has not been established for routine clinical use in ALK positive non-squamous NSCLC. The implementation of cfDNA testing may be challenging given the multiple and heterogenous mechanisms of resistance to ALK inhibitors. Based on the results of tissue biopsy testing, patients will be assigned to a specific treatment group (see Table in Section 5.1). Treatments will be selected based on preclinical and in some cases, clinical data demonstrating activity of the treatment against the specific ALK mutation or resistance mechanism identified. If no ALK-resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not received or Pemetrexed based therapy with or without cisplatin or carboplatin. The response rate in the cohort receiving chemotherapy will be compared to the response rates of each of the second-generation ALK inhibitors among patients with no ALK-resistance mutations identified.

Patients whose tissue is insufficient will need to have a repeat biopsy if feasible, as per their treating physician; otherwise, they will not be eligible for this trial. We have anticipated about 10% of patients may have insufficient tissue from a tissue biopsy for mutational testing, and have taken this into consideration when calculating sample size. cfDNA will be collected on all cases.

After the first 200 patients are enrolled, we will analyze the concordance of cfDNA and tissue biopsy. If a high degree of concordance is found with confidence, we will amend the protocol and select patients based on cfDNA only. At that time, tumor biopsy will become optional, but recommend if possible. This will be decided with input from CTEP and the FDA.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA (20-MAY-2019)

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page).

3.1 Patient Selection Guidelines (21-JUNE-2019)

3.1.1 Submission of blood and tumor tissue is required for all patients. This requirement may change to blood only after the first 200 patients have been analyzed. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See details of tissue and blood submissions in Section 10.)

3.1.2 Use of prohibited therapies listed in Appendix XIII should be taken into consideration when screening and enrolling patients in NRG-LU003. Sites will report at step 1 registration whether enrolling patients require the use of any CYP interacting agents, and any prohibited ALK inhibitors will be removed from assignment consideration for these patients

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. 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 Eligibility Criteria (17-FEB-2020)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration

3.2.1 Patients must have histologically or cytologically confirmed stage IV ALK-positive non-squamous NSCLC (includes M1a, M1b, M1c stage disease, AJCC 8th edition). ALK rearrangement must have been demonstrated by an FDA approved assay (Vysis FISH or Ventana IHC) or by next generation sequencing (NGS).

3.2.2 Patient must be willing and able to undergo a fresh biopsy, or if patient has had a biopsy after progression on current TKI within 3 months of study enrollment (and has continued TKI for clinical benefit per treating physician) this tissue may be used. Must have sufficient tissue.

3.2.3 Age ≥ 18.

3.2.4 Patient must have progressive disease as defined by RECIST 1.1 after one second generation ALK inhibitor, including LDK378 (ceritinib), alectinib, ensartinib, and brigatinib (may not have received more than one second-generation ALK inhibitor). Patient may have received prior crizotinib; however, the second generation ALK inhibitor received must be the last treatment given prior to study enrollment.

- Prior lorlatinib (third-generation ALK inhibitor) is not allowed.

3.2.5 Prior chemotherapy is not allowed except for one prior cycle received at the time of original diagnosis of metastatic NSCLC with no evidence of disease progression following the cycle. NOTE: prior adjuvant or neoadjuvant chemotherapy is allowed if last dose was received more than 12 months prior to enrollment.

3.2.6 The patient or a legally authorized representative must provide study-specific informed consent prior to Step 1 Registration.

Prior to Step 2 Registration

3.2.7 Adequate hematologic function within 28 days prior to step 2 registration defined as follows:

- ANC ≥ 1500cells/mm3
- Platelets ≥ 100,000cells/mm3

3.2.8 Adequate renal function within 28 days prior to step 2 registration defined as follows:

- Estimated creatinine clearance ≥ 60mL/min by the Cockcroft Gault formula below:

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

3.2.9 Adequate hepatic function within 28 days prior to step 2 registration defined as follows:

- Total Bilirubin ≤ 1.5 x ULN (except for patients with documented Gilbert's syndrome).

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; ≤ 5 x ULN if liver metastases are present.

3.2.10 Patients with asymptomatic treated or untreated brain metastases are eligible. Treated brain metastases are eligible as long as patients have measurable disease outside the brain according to RECIST 1.1. Patients must be on a stable or decreasing dose of steroids for at least 7 days prior to step 2 registration. Anticonvulsants are allowed as long as the patient is neurologically stable and not deteriorating.

3.2.11 Patients enrolled with asymptomatic brain mets must have at least one measurable target extracranial lesion according to RECIST 1.1.

3.2.12 ECOG performance status 0-2

3.2.13 Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤1 (except for alopecia, hearing loss).

3.2.14 Not taking any medications identified in Section 5.4.2 that may interact with selected study medication based on stratification in Section 15.1

3.2.15 Patients must be able to take oral medications (i.e. swallow whole tablets/capsules)

3.2.16 All females of childbearing potential must have a blood test or urine study within 14 days prior to Step 2 Registration to rule out pregnancy. Refer to section 9 for requirements on the length of time patients should maintain adequate contraception for after the last dose of each medication. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)
- Women must not be pregnant or breast-feeding due to potential harm to the fetus or infant from ALK inhibitors and the unknown risk. Women of childbearing potential and sexually active males must agree to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

3.3 **Ineligibility Criteria** (20-JAN-2022)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Major surgery within 2 weeks of study entry. Minor surgical procedures (eg, port insertion, pleurex catheter placement) are allowed and all wounds must not show signs of infection or draining.

3.3.2 Palliative bone RT (<10 fractions) must have been completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation must have completed at least 1 week prior to study entry. Whole brain RT or other palliative RT must have been completed at least 2 weeks prior to study entry.

3.3.3 Prior dose of second-generation ALK inhibitor (LDK378 (ceritinib), alectinib, ensartinib) within 5 days prior to step 2 registration. Prior dose of brigatinib within 7 days prior to step 2 registration.

3.3.4 History of interstitial lung disease or interstitial fibrosis, including a history of pneumonitis, obliterative bronchiolitis, pulmonary fibrosis. Patients with a history of prior radiation pneumonitis are not excluded.

3.3.5 Active inflammatory gastrointestinal disease (such as Crohns, ulcerative colitis), chronic diarrhea, symptomatic diverticular disease, or any gastrointestinal disease that would affect the absorption of oral medications or increase the risk of toxicity.

3.3.6 Clinically significant cardiovascular abnormalities, as determined by the treating/registering physician, such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia, or myocardial infarction within 6 months.

3.3.7 Active and clinically significant bacterial, fungal, or viral infection

3.3.8 Patients with active or chronic pancreatitis based on lipase elevation, symptoms, and radiographic findings

3.3.9 Other concomitant serious illness or organ system dysfunction that in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the study drug.

3.3.10 Patients must not plan to receive any other investigational agents during the course of therapy.

3.3.11 Patients with active malignancy other than ALK-positive non-squamous NSCLC within the last 2 years are excluded (note: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, papillary thyroid cancer treated with curative intent, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for 2 years are eligible).

3.3.12 No chemotherapy and/or immunotherapy allowed after step 1 registration.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

PRE-TREATMENT ASSESSMENTS (20-JAN-2022)

Assessments	Prior to Step 1 Registration	Prior to Step 2 Registration (up to 28 calendar days)
Medical history/concurrent meds		X
Physical Exam, ECOG Performance Status and vital signs (to include heart rate and blood pressure)		X
Toxicity Assessment		X
Brain MRI* (see Section 8.3 for instructions for collection of images)		X
Chest/abdomen (include pelvis if clinically indicated) CT scan contrast enhanced (see Section 8.3 instructions for collection of images)		X
EKG		X
Complete Metabolic Panel, (including creatinine, bilirubin,		X

ALT, AST, calcium, glucose, magnesium, phosphorous		
CBC with Differential (to include ANC, platelets)		X
Serum or Urine Pregnancy Test for women of childbearing potential		X (within 14 days)
Tumor biopsy**	X	
MANDATORY: Peripheral Blood (two 8.5mL Roche cell-free DNA collection tubes) see section 10 and Appendix IV for collection details **	X	
Tissue sample (for patients who consent to biobanking)	X (see section 10)	

*If contraindicated, Head CT with contrast acceptable
** Biopsy and blood taken within 3 months. If patient has a biopsy after progression on current TKI within 3 months of study enrollment (and continued TKI for clinical benefit per treating physician) this tissue may be used. Must have sufficient tissue. Note that tissue and blood samples must not be sent to Foundation Medicine, Inc. until after the patient is registered, so that unique NRG-LU003 patient identifiers may be sent with the samples. It is important to label these samples appropriately; please refer to the specimen Requisition Forms for detailed instructions. The Forms are posted on the Case Report Forms tab of the NRG-LU003 page of the CTSU website.

ASSESSMENTS DURING TREATMENT (20-JAN-2022)

Assessments	**Day 1 of Each Cycle (+/- 3 days)**	**Day 1 of Every Odd Cycle Starting with Cycle 3 (+/- 3 days)**
Medical history/Concurrent meds	X	
Physical Exam and vital signs/ECOG Performance Status	X	
Toxicity Assessment	X	
FOR PATIENTS WITH BRAIN METS: Contrast enhanced Brain MRI* (see Section 8.3 for instructions for collection of images)		X (Every 2 cycles for the first 6 months, then every 3 cycles thereafter)
FOR PATIENTS WITHOUT BRAIN METS: Contrast enhanced Brain MRI* (see Section 8.3 for instructions		As clinically indicated

for collection of images)		
Chest/abdomen (include pelvis if clinically indicated) CT scans with RECIST (see Section 13.0, and see Section 8.3 for instructions for collection of images)		X (Every 2 cycles for the first 6 months with first repeat scan prior to Cycle 3, Day 1, then every 3 cycles thereafter)
Complete Metabolic Panel, (including creatinine, bilirubin, ALT, AST, glucose**, calcium) magnesium, phosphorous	X	
Amylase, lipase	X [for patients receiving brigatinib, LDK378 (ceritinib) or lorlatinib]	
Lipid Panel (fasting)	X (for patients receiving lorlatinib only day 1 of cycles 1-3, and every 3 cycles thereafter)	
CBC with Differential	X	
CPK	X (For patients receiving alectinib and brigatinib)	
EKG		X (for patients receiving ensartinib, LDK378 (ceritinib), crizotinib and lorlatinib; as clinically indicated for alectinib and brigatinib)
Serum or Urine Pregnancy Test for women of childbearing potential	X **(CYCLE 1 ONLY)**	
MANDATORY: Peripheral Blood (two 8.5mL Roche cell-free DNA collection tubes) See Section 10 and Appendix IV for collection details		X (at progression)
Tumor biopsy (if patient consents, see Section 10)		X (at progression)***
Optional plasma collection (for patients who consent)		X (at progression)
Optional whole blood collection (for patients who consent)	X (Cycle 3, Day 1)	

*If contraindicated Head CT with contrast acceptable
**For patients receiving LDK378 (ceritinib) or brigatinib, prior to cycle 1, evaluate fasting glucose, then periodically thereafter as clinically indicated. Refer to section 6 for hyperglycemia mangagement guidelines.

***It is strongly encouraged that biopsy at time of disease progression is performed. Biopsy should be performed on a growing lesion, if available

Note: One treatment cycle will consist of 21 consecutive days

ASSESSMENTS IN FOLLOW UP (20-MAY-2019)

Assessments	30 days Post Treatment (+/- 3 days)	Long term follow up (q3 mos. x 2 years, then q6 mos. x 3 years, then annually)
Medical history/Concurrent meds	X	
Physical Exam and vital signs/ECOG Performance Status	X	
Toxicity Assessment	X	
Complete Metabolic Panel (including creatinine, bilirubin, ALT, AST, calcium, glucose) magnesium, phosphorous	X	
Amylase, lipase	X [for patients receiving brigatinib, LDK378 (ceritinib) or lorlatinib]	
CPK	X (for patients receiving alectinib or brigatinib)	
Lipid panel (fasting)	X (for patients receiving lorlatinib)	
CBC with Differential	X	
Optional whole blood collection (for patients who consent)	X	
Overall Survival		X*

* Survival status can be determined by phone and/or follow-up review of medical records.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 ALK Inhibitor Therapy (17-FEB-2020)

Table 5.1

Mutation	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG	STUDY DRUG
G1202, G1202del, G1202R	lorlatinib			brigatinib			
C1156Y	lorlatinib		alectinib	brigatinib			
I1171	lorlatinib	LDK378 (ceritinib)		brigatinib			
L1196,	lorlatinib	LDK378	alectinib	brigatinib	ensartinib		

L1196M		**(ceritinib)**					
V1180	**lorlatinib**	**LDK378 (ceritinib)**		**brigatinib**			
F1174	**lorlatinib**		**alectinib**	**brigatinib**			
Compound mutation	**lorlatinib**						
ALK L1198F (alone/ in combination with another ALK mutation.)						**crizotinib**	
MET amplification						**crizotinib**	
No ALK-resistance mutations*	**lorlatinib**	**LDK378 (ceritinib)**	**alectinib**	**brigatinib**	**ensartinib**		**Pemetrexed ± cisplatin or carboplatin**

*Including no MET amplification

Based on the identified ALK mutation(s) in tumor tissue, patients will be assigned to treatment with the indicated ALK inhibitors based the algorithm in Section 15.1. If no ALK-resistance mutations are identified, patients will be randomized to receive either a next-generation ALK inhibitor they have not received or pemetrexed with cisplatin or carboplatin. Based on emerging data from preclinical studies and early phase 1 studies, ALK-based combination strategies may be effective for those patients without on-target resistance. As safety and dosing information from these studies become available, combinations will be discussed among the steering committee members and potentially tested in the subgroup of patients without ALK resistance mutations.

All patients will receive their assigned ALK inhibitor at the standard dose. One treatment cycle for ALK inhibitors will consist of 21 consecutive days and may continue until disease progression. The treatment window for starting the initial cycle of treatment is +/- 7 days. Refer to the table of adverse events and recommended dose reductions in Section 6 prior to starting each cycle. Patients receiving pemetrexed with cisplatin or carboplatin will receive 4-6 cycles plus maintenance pemetrexed until disease progression.

All patients will undergo restaging CT chest/abdomen scans every 2 cycles for the first 6 months, and then every 3 cycles thereafter, and may undergo brain MRI imaging on treatment as clinically indicated. Responses will be evaluated locally by investigators according to RECIST v1.1. Patients may continue on treatment beyond RECIST PD if in the opinion of their treating investigator they are continuing to derive benefit from the study drug. For CNS-only relapse, patients may receive local therapy to the CNS lesion(s) and continue on study drug.

Oral Medication Adherence/Compliance Monitoring:
Patients will be asked to bring their medication bottle and a pill diary with them to each clinic visit. A pill count and evaluation of the pill diary will be completed to assess compliance. The pill diaries are located in Appendices VII and XII and on the CTSU

website.

5.2 Agent Administration (20-JAN-2022)

Protocol treatment must begin within 2 weeks after Step 2 Registration.

All patients will receive their assigned ALK inhibitor at the standard dose. All ALK inhibitors are orally administered. Starting doses and dose reductions are summarized in Section 6. One treatment cycle will consist of 21 consecutive days. Treatment will continue until disease progression or unacceptable toxicity.

5.2.1 ALK Inhibitors

If a dose is missed or vomiting occurs after dosing, do not administer an additional dose and take the next dose at the schedule time.

A dose is considered missed after 6 hours for a drug that is dosed twice a day, or after 12 hours for a drug that is dosed once a day.

Alectinib

Administration: 600 mg orally twice daily with food at similar times each day (i.e. breakfast and dinner); administer until disease progression or unacceptable toxicity.

Do not open or dissolve capsule contents.

LDK378 (ceritinib)

Administration: 450 mg orally once a day with food; administer until disease progression or unacceptable toxicity.

If a dose is missed or vomiting occurs after dosing, do not administer an additional dose and continue with the next scheduled dose of LDK378 (ceritinib).

Brigatinib

Administration: 90 mg orally once a day for the first 7 days; if tolerated, with no respiratory symptoms, increase the dose to 180 mg once daily; administer until disease progression or unacceptable toxicity.

If brigatinib is delayed for 14 days or longer for reasons other than toxicity, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

Brigatinib may be taken with or without food; do not crush or chew tablets, swallow whole.

Ensartinib

Administration: 225 mg orally once a day with or without food; administer until disease progression or unacceptable toxicity.

Lorlatinib

Administration: 100 mg orally once a day with or without food or beverage; administer until disease progression or unacceptable toxicity.

Crizotinib
Administration: 250 mg orally twice daily; administer until disease progression or unacceptable toxicity.

Crizotinib may be taken with or without food. Swallow capsules whole. Do not open or dissolve capsule contents. If vomiting occurs after dosing, do not administer an additional dose and continue with the next scheduled dose of crizotinib.

5.2.2 Pemetrexed based chemotherapy with cisplatin or carboplatin
Administration: Pemetrexed 500 mg/m^2 administered by IV over 10 minutes on Day 1 of a 21 day cycle with cisplatin or carboplatin. Doses can be rounded per institution policy.
NOTE: Pemetrexed administration requires vitamin supplementation initiated one week prior to first dose of pemetrexed with the following:

- Folic acid 1000 mcg PO once daily continuously for duration of chemotherapy and should continue for 21 days after last dose of pemetrexed.
- Administer vitamin B, B12, 1000 mcg IM intramuscularly, 1 week prior to the first dose of pemetrexed and every 9 weeks.
- Administer dexamethasone per institutional guidelines

Cisplatin
Administration: 75 mg/m^2 IV once every 3 weeks (on Day 1 of a 21 day cycle with pemetrexed). Prepare and administer per institution policy. Doses can be rounded per institution policy.

Carboplatin
Administration: AUC5 once every 3 weeks (on Day 1 of a 21 day cycle with pemetrexed). Prepare and administer per institution policy. Doses can be rounded per institution policy. Carboplatin dose will be calculated using the Calvert formula. For the purposes of this protocol, the glomerular filtration rate is considered equivalent to the creatinine clearance calculated by Cockcroft-Gault and is capped at 125 mL/min.

Duration of Treatment: Patients will initially receive 4-6 cycles of pemetrexed with cisplatin or carboplatin.

5.2.3 Maintenance Pemetrexed
Maintenance treatment of pemetrexed (as a single agent) may continue until progression or significant toxicity as determined by clinical findings through physical examination, imaging, etc.

5.3 Integrated Assay/Biomarker (20-May-2019)
FoundationOne®CDx utilizes a hybrid-capture, next-generation sequencing testing method on solid tissue biopsies.
FoundationOne®Liquid utilizes a hybrid-capture, next-generation sequencing testing

method on liquid (blood) biopsies.

For further information related to technical specifications and sample processing, please refer to Appendices I-IV.

The first 200 patients enrolled into the trial will be randomized, described in Section 15.1, based upon NGS from baseline FoundationOne®CDx testing. Concomitant concordance testing will occur with the FoundationOne®Liquid assay to determine whether subsequent patients enrolled into the trial can be randomized based upon baseline blood-based genomic testing as opposed to tissue-based testing.

5.4 General Concomitant Medication and Supportive Care Guidelines (20-JAN-2022)

5.4.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

- Anticonvulsants
- Antiemetics may be administered according to standard practice.
- Anticoagulants
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Highly active antiretroviral therapy (HAART)
- Supported therapies for toxicities associated with pemetrexed, according to the FDA approved label or institutional practice.

5.4.2 Prohibited Concomitant Therapies (by Agent)

- Alectinib
  - None
- Brigatinib
  - Avoid concomitant use of brigatinib with strong CYP3A inhibitors or inducers.
  -
  - As brigatinib inhibits P-gp, BCRP, OCT1, MATE1, MATE2k, and induces CYP3A and 2C, use caution with administered agents that are P-gp, BCRP, OCT1, MATE1, MATE2K, CYP3A, or 2C substrates.
- LDK378 (ceritinib)
  - Avoid concurrent use of LDK378 (ceritinib) with strong CYP3A4/5 inhibitors or inducers; avoid concurrent use of certitinib with CYP3A4/5 or CYP2C9 substrates with narrow therapeutic indices.
  - Co-administration of medications with known potential for QTc prolongation should be avoided.
- Crizotinib
  - Avoid concurrent use of crizotinib with strong CYP3A inhibitors or inducers. Avoid concurrent use of crizotinib with CYP3A4/5 substrates with narrow therapeutic indices.

- Ensartinib
  To be used with caution:
  - Drugs that are CYP3A4/5 substrates with narrow therapeutic indices.
  - Drugs that are strong CYP3A4/5 inhibitors.
  - Drugs that are strong CYP3A4/5 inducers
  - Concomitant treatment with medications with a known risk for Torsades de Pointes should be used with caution.
  - As ensartinib inhibits CYP2C9, drugs metabolized by CYP2C9 with narrow therapeutic indices should be used with caution.
- Lorlatinib
  - Strong CYP3A inducers are contraindicated.
  - Avoid concomitant use with moderate CYP3Ainducers.
  - Avoid concomitant use with strong CYP3A inhibitors.
  - Avoid concomitant use of lorlatinib with CYP3A substrates with narrow therapeutic indices.
  - Avoid concomitant use of lorlatinib with P-gp substrates with narrow therapeutic indices.
- Pemetrexed with cisplatin or carboplatin
  - Ibuprofen increases exposure (AUC) of pemetrexed. Avoid administration of ibuprofen for 2 days before, the day of and 2 days following administration of pemetrexed. Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

Because there is a potential for interaction 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 study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix XIV (Patient Drug Information Handout and Wallet Card for Ensartinib) should be provided to patients assigned to ensartinib. Appendix XV (Patient Clinical Trial Wallet Card) should be provided to all other patients.

5.4.3 Participation in Other Trials

Participation in other clinical trials of anti-neoplastic therapy is not allowed.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in 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.

Progression is determined based on RECIST 1.1. Patients will be allowed to continue on study treatment beyond RECIST defined PD if the treating investigator believes the patient is deriving clinical benefit. Response is determined by RECIST 1.1.

6. TREATMENT MODIFICATIONS/MANAGEMENT

For all drugs, permanently discontinue if treatment is held for greater than 21 days with or without resolution of toxicity. Only up to two dose reductions are allowed and dose re-escalation is not allowed.

ALK inhibitor	Starting dose	First dose reduction	Second dose reduction
Alectinib	600 mg PO twice daily	450 mg PO twice daily	300 mg PO twice daily
LDK378 (ceritinib)	450 mg PO once daily	300 mg PO once daily	150 mg PO once daily
Brigatinib	90 mg PO once daily x 1 week	60 mg once daily	Permanently discontinue
	180 mg PO once daily	120mg once daily	90 mg PO once daily
Ensartinib	225 mg PO once daily	200 mg PO once daily	150mg PO once daily
Lorlatinib	100 mg PO once daily	75 mg PO once daily	50 mg PO once daily
Crizotinib	250 mg PO twice daily	200 mg PO twice daily	250 mg PO once daily
Pemetrexed	500 mg/m^2 IV once every 3 weeks	375 mg/m^2 IV once every 3 weeks..	250 mg/m^2 IV once every 3 weeks..
Cisplatin	75 mg/m^2 IV once every 3 weeks	60 mg/m^2 IV once every 3 weeks	48 mg/m^2 IV once every 3 weeks
Carboplatin	AUC5 once every 3 weeks	AUC=4 once every 3 weeks	AUC=3.2 once every 3 weeks

6.1 Dose Modifications and Toxicity Management for Alectinib

Hepatic Toxicity	
Grade	**Dose Modification**
Grade 3 AST or ALT elevation of greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 3 times ULN, then dose will be reduced by one dose level, per table in section 6.
Grade 2 ALT or AST elevation greater than 3 times ULN with total bilirubin	Permanently discontinue alectinib.

elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	
Grade 3 Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then dose will be reduced by one level as per section 6.
Interstitial Lung Disease/Pneumonitis	
Grade	**Dose Modification**
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue alectinib.
Renal Toxicity	
Grade	**Dose Modification**
Grade 3 renal impairment	Temporarily withhold until serum creatinine recovers to less than or equal to 1.5 times ULN, then dose will be reduced by one level.
Grade 4 renal impairment	Permanently discontinue alectinib.
Cardiac Toxicity	
Grade	**Dose Modification**
Grade 2 or Grade 3 Symptomatic sinus bradycardia	Withhold alectinib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume alectinib at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume alectinib by reducing one dose level (see section 6) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Grade 4 Sinus bradycardia (life-threatening consequences, urgent intervention indicated)	Permanently discontinue alectinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume alectinib by reducing one dose level (see section 6) upon

	recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue alectinib in case of recurrence.
Blood Creatinine Phosphokinase (CPK)	
Grade	**Dose Modification**
Grade 3 CPK elevation greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
Grade 4 CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then reduce by one dose level per section 6.

6.2 Dose Modifications and Toxicity Management for Brigatinib

Avoid concomitant use of strong CYP3A inhibitors during treatment with brigatinib. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the brigatinib once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, resume the brigatinib dose that was tolerated prior to initiating the strong CYP3A inhibitor.

Interstitial Lung Disease (ILD)/Pneumonitis	
Grade	**Dose Modification**
Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue brigatinb
Grade 2	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold brigatinib until recovery to baseline. Resume at next lower dose (per section 5.1.1) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold brigatinib until recovery to baseline. If ILD/pneumonitis is suspected, resume

	at next lower dose (section 6); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue
Grade 3 or 4	Permanently discontinue brigatinib for ILD/pneumonitis
Hypertension	
Grade	**Dose Modification**
Grade 3	• Withhold brigantinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume brigatinib at next lower dose (section 6). • Recurrence: withhold brigatinib until recovery to Grade 1 or less, and resume at next lower dose (section 6) or permanently discontinue treatment.
Grade 4	• Withhold brigatinib until recovery to Grade 1 or less, and resume at next lower dose (section 6) or permanently discontinue treatment. • Recurrence: permanently discontinue brigatinib for recurrence of Grade 4 hypertension.
Bradycardia (HR less than 60 bpm)	
Grade	**Dose Modification**
Grade 2 or Grade 3 Symptomatic sinus bradycardia	• Withhold brigatinib until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume brigatinib at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume brigatinib at next lower dose (see section 6) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
Grade 4	• Permanently discontinue brigatinib if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume brigatinib at next lower dose (see section 6) upon recovery to

	asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue brigatinib
Visual Disturbances	
Grade	**Dose Modification**
Grade 2 or 3 visual disturbance	Withhold brigatinib until recovery to Grade 1 or baseline, then resume at the next lower dose (see section 6)
Grade 4 visual disturbance	Permanently discontinue brigatinib
Creatinine Phosphokinase (CPK) Elevation	
Grade	**Dose Modification**
Grade 3	Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 x ULN) or to baseline, then resume brigatinib at same dose
Grade 4 or recurrence of Grade 3 elevation	Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume brigatinib at next lower dose (see section 6)
Lipase or Amylase Elevation	
Grade	**Dose Modification**
Grade 3	Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume brigatinib at same dose.
Grade 4 or recurrence of Grade 3	Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume brigatinib at next lower dose (see section 6)
Hyperglycemia	
Grade	**Dose Modification**
Grade 3 or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold brigatinib until adequate hyperglycemic control is achieved and consider reduction to the next dose (see section 6) or permanently discontinue brigatinib.
Other Toxicity related to Brigatinib	
Grade	**Dose Modification**
Grade 3	• Withhold brigatinib until recovery to baseline, then resume at same dose.

	• Recurrence: withhold brigatinib until recovery to baseline, then resume at next lower dose or discontinue brigatinib (see section 6).
Grade 4	• First occurrence: either withhold brigatinib until recovery to baseline and resume at next lower dose (see section 6) or permanently discontinue. • Permanently discontinue brigatinib for recurrence.

6.3 Dose Modifications and Toxicity Management for LDK378 (ceritinib)

Gastrointestinal Adverse Reaction	
Grade	**Dose Modification**
Grade 2 Lipase or amylase increase	Withhold and monitor serum lipase and amylase. Resume LDK378 (ceritinib) with a 150mg dose reduction after recover to less than 1.5 times ULN.
Grade 3 or greater, severe or intolerable nausea, vomiting or diarrhea despite optimal antiemetic or antidiarrheal therapy	Withhold until improved, then resume LDK378 (ceritinib) with a 150 mg dose reduction.
Hyperglycemia	
Grade	**Dose Modification**
Grade 3 despite optimal antihyperglycemic therapy	Withhold until hyperglycemia is adequately controlled, then resume LDK378 (ceritinib) with a 150 mg dose reduction. If adequate hyperglycemic control cannot be achieved with optimal medical management, discontinue LDK378 (ceritinib).
Pneumonitis	
Grade	**Dose Modification**
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue LDK378 (ceritinib)
Cardiac Arrhythmias	
Grade	**Dose Modification**
Grade 3 QT corrected interval prolonged QTc interval $\geq$ 500 ms	Withhold until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to

	481 msec, then resume LDK378 (ceritinib) with a 150 mg dose reduction
Grade 4 QTc QT corrected interval prolonged	Permanently discontinue LDK378 (ceritinib).
Grade 2 Symptomatic bradycardia	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate concomitant medications known to cause bradycardia, and resume LDK378 (ceritinib) with a 150mg dose reduction, with frequent monitoring.
Grade 3 Clinically significant bradycardia requiring intervention or Grade 4 life-threatening bradycardia in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If the concomitant medication can be adjusted or discontinued, resume certinib with a 150 mg dose reduction, with frequent monitoring.
Grade 4 Life-threatening bradycardia in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension	Permanently discontinue LDK378 (ceritinib).
Hepatotoxicity	
Grade	**Dose Modification**
Grade 3 ALT or AST elevation greater than 5 times ULN with total bilirubin elevation less than or equal to 2 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume LDK378 (ceritinib) with a 150 mg dose reduction.
Grade 2 ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue LDK378 (ceritinib).

6.3.1 LDK378 (ceritinib) Dose Modification for Strong CYP3A Inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with LDK378 (ceritinib). If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the LDK378 (ceritinib) dose by one dose level. After discontinuation of a strong CYP3A inhibitor, resume the LDK378 (ceritinib) dose that was taken prior to initiating the strong CYP3A inhibitor.

6.4 Dose Modifications and Toxicity Management for Crizotinib

Hematologic Toxicities*	
Grade	**Dose Modification**
Grade 3	Withhold until recovery to Grade 2 or less, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade 2 or less, then resume at next lower dose

* Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Hepatotoxicity	
Grade	**Dose Modification**
Grade 3 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at reduced dose.
Grade 2 ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue.
ILD/Pneumonitis	
Grade	**Dose Modification**
Any grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue.
Cardiac Toxcitity	
Grade	**Dose Modification**
Grade 3 QT corrected interval prolonged	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at reduced dose.
Grade 4 QT corrected interval prolonged	Permanently discontinue.
Grade 2 or Grade 3 Bradycardia* (symptomatic, may be severe and medically	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.

significant, medical intervention indicated)	Evaluate concomitant medications known to cause bradycardia, as well as antihypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Grade 4 Bradycardia*,† (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.
Visual Toxicity	
Grade	**Dose Modification**
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe vision loss.

*Heart rate less than 60 beats per minute (bpm).
†Permanently discontinue for recurrence.

6.5 Dose Modifications and Toxicity Management for Ensartinib

Drug-related Hematologic Toxicities	
Grade	**Dose Modification***
Grade 3 ANC decrease	Withhold ensartinib until recovery to Grade ≤ 2, then resume at the same dose level.
Grade 4 ANC decrease	Withhold ensartinib until recovery to ≤ Grade 2, then resume at a one dose level reduction.
Grade 3 Platelet count decrease	Withhold ensartinib until recovery to ≤ Grade 2, then resume at the same dose level.
Grade 4 Platelet count decrease	Withhold ensartinib until recovery to ≤ Grade 2, then resume at a one dose level reduction.
Drug-related Non-Hematologic Toxicities	

Transaminase Elevations	
Grade	**Dose Modification***
Grade 3 ALT or AST elevation > 5 times ULN with total bilirubin elevation ≤ 2x ULN	Withhold ensartinib until recovery to baseline or ≤ 3x ULN, then resume at a one dose level reduction.
Grade 2 ALT or AST elevation > 3x ULN in conjunction with total bilirubin elevation > 2x ULN (in absence of cholestasis or hemolysis), and no correctable, non-drug related cause	Permanently discontinue ensartinib
Pneumonitis	
Grade	**Dose Modification***
Pneumonitis of any grade**	Permanently discontinue ensartinib
Rash***	
Grade	**Dose Modification***
Grade 1 (mild)	Continue ensartinib at same dose, follow, and, if necessary, use topical treatments.
Grade 2 (moderate and symptomatic)	Continue ensartinib at same dose; topical corticosteroids may be used. If, after 1 week, the rash is worse or there is no improvement, give a 5 day course of tapering oral corticosteroids. If, one week later, it is not improved to at least mild (≤ Grade 1), withhold ensartinib until at least mild (≤ Grade 1). At that time, resume ensartinib at a one dose level reduction.
Grade 3 (severe)	Withhold ensartinib. Topical treatments may be used. Oral corticosteroids may be considered. When improved to at least mild (≤ Grade 1), resume ensartinib at a one dose level reduction.
Nausea, Vomiting and Diarrhea	
Grade	**Dose Modification***
Grade 3 or greater	Withhold ensartinib and initiate supportive care. If Grade 3 toxicity lasts ≤ 7 days, resume ensartinib at a one dose level reduction when toxicity recovers to ≤ Grade 1.
QTcF Prolongation	
Grade	**Dose Modification**
QTcF >500 ms on at least 2 separate ECGs	Withhold until recovery to baseline or to a QTcF <481 ms, then resume at one dose level reduction.
QTcF >500 ms or ≥60 ms change from baseline with Torsade de pointes or	Permanently discontinue.

polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	
Bradycardia	
Grade	**Dose Modification**
Bradycardia: heart rate <60 beats per minute (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. Evaluate concomitant medications known to cause bradycardia, as well as antihypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at one level dose reduction upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia: recurrent heart rate <60 beats per minute (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at one level dose reduction upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.
Visual Loss	
Grade	**Dose Modification**
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe vision loss. Any patient that experiences severe visual loss (best corrected vision less than 20/200 in one or both eyes) or other serious visual complaints should have an ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss. There is insufficient information to characterize the risks of resumption of treatment in patients with a severe visual loss; a decision to resume treatment should consider the potential benefits to the patient.
Severe Renal Dysfunction	
Grade	**Dose Modifications**
Severe renal dysfunction (CL <30 mL/min) not requiring dialysis (not thought to be related to study medication)	Hold dose until creatinine clearance returns to < grade 3 (CL ≥30 mL/min). If this occurs within 4 weeks, resume at a 1 level dose reduction. When CL improves to ≥50 mL/min, dose may be escalated back

	to the pre-dose modification level, if appropriate.
Grade 3 renal dysfunction not requiring dialysis (thought to be study drug-related) and expected to be manageable and reversible with dose reduction	Withhold ensartinib until recovery to ≤ Grade 1. If toxicity remains Grade 3 for > 7 days, permanently discontinue ensartinib*. If Grade 3 toxicity lasts ≤ 7 days and resolves to ≤ Grade 1, resume at a one dose level reduction.
Grade 3 renal dysfunction not requiring dialysis (thought to be study drug-related) and not expected to be manageable and reversible with dose reduction	Permanently discontinue ensartinib.
Grade 4 renal dysfunction not requiring dialysis (thought to be study drug-related)	Permanently discontinue ensartinib.
Other Toxicity related to Ensartinib	
Grade	**Dose Modification***
Grade 3 and expected to be manageable and reversible with dose reduction	Withhold ensartinib. If toxicity remains Grade 3 for > 7 days, permanently discontinue ensartinib*. If Grade 3 toxicity lasts ≤ 7 days and resolves to baseline or ≤ Grade 1, resume at a one dose level reduction.
Grade 3 and not expected to be manageable and reversible with dose reduction	Permanently discontinue ensartinib
Recurrence of Grade 3 toxicity	Withhold ensartinib until resolves to baseline or ≤ Grade 1, then resume at a one dose level reduction or permanently discontinue ensartinib.
Grade 4	Permanently discontinue ensartinib*

* Any patient who develops toxicity that does not resolve to baseline or ≤ Grade 1 within 4 weeks or requires a treatment delay of more than 4 weeks due to treatment-related toxicity should be discontinued from trial treatment. In the case of either Grade 3 toxicity lasting longer than 7 days or Grade 4 toxicity, if the investigator feels that it is appropriate for the patient to continue treatment with ensartinib, this may be allowed after discussion with the Study Chair.
** For pneumonitis of any grade not attributable to other causes, such as NSCLC progression, other pulmonary disease, infection, or radiation effect, discontinue ensartinib.
*** For rash severity, rather than using CTCAE criteria based on BSA, consider severity based on symptoms and intensity.

6.6 Dose Modifications and Toxicity Management for Lorlatinib

Central Nervous System Effects	
Grade	**Dose Modification**

Grade 1	Continue at the same dose or withhold the dose until recovery to baseline. Resume lorlatinib at the same dose or at a reduced dose.
Grade 2 OR Grade 3	Withhold dose until Grade 0 or 1. Resume lorlatinib at a reduced dose.
Grade 4	Permanently discontinue lorlatinib.
Hyperlipidemia	
Grade 4 hypercholesterolemia OR Grade 4 hypertriglyceridemia	Withhold lorlatinib until recovery of hypercholesterolemia and/or hypertriglyceridemia to less than or equal to Grade 2. Resume lorlatinib at the same dose. If severe hypercholesterolemia and/or hypertriglyceridemia recurs, resume lorlatinib at a reduced dose.
Atrioventricular (AV) Block	
Second-degree AV block	Withhold lorlatinib until PR interval is less than 200 ms. Resume lorlatinib at a reduced dose.
First occurrence of complete AV block	Withhold lorlatinib until • pacemaker placed OR • PR interval less than 200 ms. If a pacemaker is placed, resume lorlatinib at the same dose. If no pacemaker is placed, resume lorlatinib at a reduced dose.
Recurrent complete AV block	Place pacemaker or permanently discontinue lorlatinib.
Interstitial Lung Disease (ILD)/Pneumonitis	
Any Grade treatment–related ILD/Pneumonitis	Permanently discontinue lorlatinib.
Other Adverse Reactions	
Grade 1 OR Grade 2	Continue lorlatinib at same dose or reduced dose.

Grade 3 OR Grade 4	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Resume lorlatinib at one level dose reduction.

6.7 Dose Modifications and Toxicity Management for Pemetrexed

Adverse Event	Dose Modification
Myelosuppressive toxicity	
ANC less than 500 mm^3 and platelets greater than or equal to 50,000/mm^3 OR Platelet count less than 50,000/mm^3 without bleeding.	Hold dose until recovered then 375 mg/m^2
Platelet count less than 50,000/mm^3 with bleeding	Hold dose until recovered then 250 mg/m^2
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	
Any Grade 3 or 4 toxicities EXCEPT mucositis or neurologic toxicity OR Diarrhea requiring hospitalization	Hold dose until recovered then 375 mg/m^2
Grade 3 or 4 mucositis	Hold dose until recovered then 250 mg/m^2
Renal toxicity	Withhold until creatinine clearance is 45 mL/min or greater
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue
Severe and life-threatening Skin Toxicity	Permanently discontinue
Interstitial Pneumonitis	Permanently discontinue

6.8 Dose Modifications and Toxicity Management for Cisplatin

The table below is recommended dose adjustments for cisplatin.

Adverse Event	Dose Modification
Myelosuppressive toxicity	
ANC less than 500 mm^3 OR Platelet count less than 50,000/mm^3 without bleeding.	Hold dose until recovered then 60 mg/m^2
Platelet count less than 50,000/mm^3 with bleeding	Hold dose until recovered then 37.5 mg/m^2
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	
Any Grade 3 or 4 toxicities	Hold dose until recovered then 48 mg/m^2
Renal toxicity	CrCl 46-60 mL/min give 75% dose (56 mg/m^2) CrCl 30-45 mL/min give 50% dose (37.5mg/m^2) < 30 mL/min - discontine
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue

6.9 Dose Modifications and Toxicity Management for Carboplatin

The table below is recommended dose adjustments for carboplatin.

Adverse Event	Dose Modification
Myelosuppressive toxicity	
ANC less than 500 mm^3 OR Platelet count less than 75,000/mm^3 without bleeding.	Hold dose until recovered then AUC=4
Platelet count less than 50,000/mm^3 with bleeding	Hold dose until recovered then AUC =3.2
Recurrent Grade 3 or 4 myelosuppression after 2 dose reductions	Discontinue
Non-hematologic toxicity	

Any Grade 3 or 4 toxicities	Hold dose until recovered then AUC = 3.2
Grade 3 or 4 neurologic toxicity	Permanently discontinue
Recurrent Grade 3 or 4 non-hematologic toxicity after 2 dose reductions	Permanently discontinue

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agents administered in NRG-LU003 are being made available under an IND sponsored by CTEP. For lorlatinib, LDK378 (ceritinib), alectinib, brigatinib, crizotinib, and ensartinib determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs and routine reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.2.3 Adverse Events of Special Interest for Alectinib

The following adverse events must be reported expeditiously within 24h of awareness regardless of grade or seriousness criteria:

Drug-Induced Liver Injury (DILI)

Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice as defined by Hy's Law

[The finding of an elevated ALT or AST (> 3 times baseline value) in combination with either an elevated total bilirubin (> 2 times ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury].

Suspected Transmission of an Infectious Agent by the Study Treatment
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic.is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for CTEP Study Agents (20-JAN-2022)

7.3.1 Alectinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Alectinib hydrochloride (NSC 794611)

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 891 patients.* Below is the CAEPR for Alectinib hydrochloride.

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 2.1, October 24, 2018[1]

Adverse Events with Possible Relationship to Alectinib hydrochloride (CTCAE 5.0 Term) [n= 891]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		

Adverse Events with Possible Relationship to Alectinib hydrochloride (CTCAE 5.0 Term) [n= 891]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC DISORDERS			
	Sinus bradycardia		
EYE DISORDERS			
	Eye disorders - Other (vision disorders)[2]		
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
Constipation			***Constipation (Gr 2)***
	Diarrhea		
	Mucositis oral		
	Nausea		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
		Generalized edema	
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (drug-induced liver injury)	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	CPK increased		***CPK increased (Gr 2)***
	Creatinine increased		

Adverse Events with Possible Relationship to Alectinib hydrochloride (CTCAE 5.0 Term) [n= 891]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Neutrophil count decreased		
	Weight gain		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		*Myalgia (Gr 2)*
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Photosensitivity		
	Rash maculo-papular		

[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]Vision disorders including diplopia, photopsia, vision blurred, visual impairment, and vitreous floaters have been reported with several ALK inhibitors.

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

CARDIAC DISORDERS - Sinus tachycardia
GASTROINTESTINAL DISORDERS - Abdominal pain; Enterocolitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; Malaise; Pain
INFECTIONS AND INFESTATIONS - Bladder infection; Bronchial infection; Lung infection; Pharyngitis; Sepsis; Urinary tract infection
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T-wave abnormal; GGT increased; Lymphocyte count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Anorexia; Glucose intolerance;

Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hyperammonemia); Metabolism and nutrition disorders - Other (malnutrition)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Musculoskeletal and connective tissue disorder - Other (hemiparesis)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Dizziness; Edema cerebral; Nervous system disorders - Other (cerebral ventricle dilatation); Seizure; Stroke; Syncope
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disorder)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Pruritus
VASCULAR DISORDERS - Thromboembolic event

Note: Alectinib hydrochloride 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.

7.3.2 Brigatinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Brigatinib (AP26113, NSC 784728)

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 492 patients.* Below is the CAEPR for Brigatinib (AP26113).

> **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 2.2, May 7, 2020[1]

Adverse Events with Possible Relationship to Brigatinib (AP26113) (CTCAE 5.0 Term) [n= 492]			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)***
CARDIAC DISORDERS			
		Sinus bradycardia	
EYE DISORDERS			
		Eye disorders - Other (visual disturbances)[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
INFECTIONS AND INFESTATIONS			
		Lung infection	
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)***
	Lipase increased		***Lipase increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Serum amylase increased		***Serum amylase increased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		***Muscle cramp (Gr 2)***

Adverse Events with Possible Relationship to Brigatinib (AP26113) (CTCAE 5.0 Term) [n= 492]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (neoplasm progression, lung adenocarsinoma)		
NERVOUS SYSTEM DISORDERS			
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Hypoxia	
		Pleural effusion	
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (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]Visual disturbances includes altered visual depth perception, asthenopia, cataract, color blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular edema, photophobia, photopsia, retinal edema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, and vitreous floaters.

[3]Generalized edema includes eyelid edema, face edema, localized edema, edema peripheral, periorbital edema, and swelling face.

Adverse events reported on brigatinib (AP26113), but for which there is insufficient evidence to suggest that there was a reasonable possibility that brigatinib (AP26113) caused the adverse event:

CARDIAC DISORDERS - Palpitations; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Flatulence; Gastric hemorrhage; Mucositis oral; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Fever; Generalized edema[3]; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
INFECTIONS AND INFESTATIONS - Meningitis; Sepsis; Upper respiratory infection; Urinary tract infection
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood lactate dehydrogenase increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (hyperinsulinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Musculoskeletal and connective tissue disorder - Other (musculoskeletal chest pain, musculoskeletal stiffness); Myalgia; Pain in extremity
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Memory impairment; Nervous system disorders - Other (peripheral neuropathy); Stroke
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Photosensitivity; Pruritus; Rash acneiform
VASCULAR DISORDERS - Thromboembolic event

Note: Brigatinib (AP26113) 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.

7.3.3 LDK378 (ceritinib)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for LDK378 (ceritinib, NSC 802646)

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 1770 patients.* Below is the CAEPR for LDK378 (ceritinib).

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 2.1, October 2, 2019[1]

Adverse Events with Possible Relationship to LDK378 (ceritinib) (CTCAE 5.0 Term) [n= 1770]			**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)***
CARDIAC DISORDERS			
		Sinus bradycardia	
EYE DISORDERS			
	Eye disorders - Other (vision disorders)		
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatotoxicity)[2]	
INFECTIONS AND INFESTATIONS			
	Lung infection		
	Upper respiratory infection		
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***

Adverse Events with Possible Relationship to LDK378 (ceritinib) (CTCAE 5.0 Term) [n= 1770]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
		Blood bilirubin increased	
	Creatinine increased Electrocardiogram QT corrected interval prolonged		***Creatinine increased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Lipase increased Lymphocyte count decreased		***Lymphocyte count decreased Gr 4)***
	Serum amylase increased		
Weight loss			***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***

Adverse Events with Possible Relationship to LDK378 (ceritinib) (CTCAE 5.0 Term) [n= 1770]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Photosensitivity	
	Skin and subcutaneous disorders - Other (rash)[3]		***Skin and subcutaneous disorders - Other (rash)*** [3] ***(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]Hepatoxicity includes Drug-induced liver injury, Hepatitis cholestatic, Hepatocellular injury, and Liver injury.

[3]Rash includes Dermatitis acneiform and Rash maculo-papular.

Adverse events reported on LDK378 (ceritinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that LDK378 (ceritinib) caused the adverse event:

CARDIAC DISORDERS - Cardiac disorders - Other (atrioventricular block); Cardiac disorders - Other (bundle branch block right); Cardiac disorders - Other (electrocardiogram Qrs complex prolonged); Pericarditis; Ventricular arrhythmia
GASTROINTESTINAL DISORDERS - Dyspepsia Dysphagia; Gastroesophageal reflux disease; Mucositis oral
HEPATOBILIARY DISORDERS - Hepatic pain; Hepatobiliary disorders - Other (hepatitis, hepatitis acute); Hepatobiliary disorders - Other (hepatic function abnormal)
INVESTIGATIONS - Investigations - Other (ammonia increased); Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia
NERVOUS SYSTEM DISORDERS - Seizure
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash acneiform[3]

Note: LDK378 (ceritinib) 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.

7.3.4 Crizotinib (Xalkori®, PF-02341066)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for Crizotinib (PF-02341066, NSC 749005)

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 2058 patients.* Below is the CAEPR for Crizotinib (PF-02341066).

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 2.3, October 30, 2018[1]

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			**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)***
		Febrile neutropenia	
CARDIAC DISORDERS			
		Heart failure	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
		Testosterone deficiency	
EYE DISORDERS			
Eye disorders - Other (vision disorders)[2]			***Eye disorders - Other (vision disorders)[2] (Gr 2)***
Periorbital edema			***Periorbital edema (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colonic perforation	
Constipation			***Constipation (Gr 2)***

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Esophageal ulcer	
		Esophagitis	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema face			***Edema face (Gr 2)***
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Generalized edema			***Generalized edema (Gr 2)***
Localized edema			***Localized edema (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (hepatotoxicity)	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
		Blood bilirubin increased	
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		
	Nervous system disorders - Other (neuropathy)[3]		***Nervous system disorders - Other (neuropathy)[3] (Gr 2)***
		Syncope	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal cyst)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[4]		

[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]Vision disorders may include the following: Chromatopsia, Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Vitreous floaters, and Visual perseveration.

[3]Neuropathy may include the following: Acute polyneuropathy, Amyotrophy, Areflexia, Autoimmune neuropathy, Autonomic failure syndrome, Autonomic neuropathy, Axonal neuropathy, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Decreased vibratory sense, Demyelinating polyneuropathy, Dysesthesia, Electromyogram abnormal, Formication, Gait disturbance, Genital hypoesthesia, Guillain-Barre syndrome,

Hyperesthesia, Hypoesthesia, Hyporeflexia, Hypotonia, Ischemic neuropathy, Loss of proprioception, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Motor dysfunction, Multifocal motor neuropathy, Muscle atrophy, Muscular weakness, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuralgia, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuropathy peripheral, Neuropathy vitamin B6 deficiency, Neurotoxicity, Paresthesia, Peripheral motor neuropathy, Peripheral nerve lesion, Peripheral nerve palsy, Peripheral nervous system function test abnormal, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal muscular atrophy, Peroneal nerve palsy, Phrenic nerve paralysis, Polyneuropathy, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Radiation neuropathy, Sensorimotor disorder, Sensory disturbance, Sensory loss, Skin burning sensation, Temperature perception test decreased, Tinel's sign, Toxic neuropathy, and Ulnar neuritis.

[4]Treatment-related rash may include erythematous rash, rash maculo-papular, and pruritus.

Adverse events reported on crizotinib (PF-02341066) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that crizotinib (PF-02341066) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (basophilia); Disseminated intravascular coagulation; Eosinophilia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Myocarditis; Pericardial effusion; Supraventricular tachycardia
EYE DISORDERS - Cataract; Optic nerve disorder; Papilledema
GASTROINTESTINAL DISORDERS - Colitis; Dysphagia; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal amyloidosis); Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; General disorders and administration site conditions - Other (failure to thrive); Malaise; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatitis)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INFECTIONS AND INFESTATIONS - Abdominal infection; Infections and infestations - Other (peridiverticular abscess); Kidney infection; Lung infection; Sepsis; Skin infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (traumatic lung injury); Spinal fracture; Wound complication
INVESTIGATIONS - Blood lactate dehydrogenase increased; CPK increased; GGT increased; Investigations - Other (monocyte count increased); Investigations - Other (platelet count increased); Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia;

Musculoskeletal and connective tissue disorder - Other (myopathy); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Pyramidal tract syndrome; Seizure; Stroke
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Pregnancy loss
PSYCHIATRIC DISORDERS - Confusion; Delirium; Euphoria
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal calculi; Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hematoma; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

Note: Crizotinib (PF-02341066) 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.

7.3.5 Ensartinib

NOTE: This study is closed to accrual and patients who received ensartinib are no longer receiving treatment; therefore the CAEPR will not be further updated.

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Ensartinib (X-396 hydrochloride, NSC 784729)

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 490 patients.* Below is the CAEPR for Ensartinib (X-396 hydrochloride).

> **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.

Adverse Events with Possible Relationship to Ensartinib (X-396 hydrochloride) (CTCAE 5.0 Term) [n= 490]			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)***
CARDIAC DISORDERS			
	Sinus bradycardia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation Diarrhea		***Constipation (Gr 2)*** ***Diarrhea (Gr 2)***
	Mucositis oral		
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face		
	Edema limbs		
	Fatigue		***Fatigue (Gr 2)***
	Fever		
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	CPK increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
	GGT increased		
	Investigations - Other (neutrophil count increased)		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***

Adverse Events with Possible Relationship to Ensartinib (X-396 hydrochloride) (CTCAE 5.0 Term) [n= 490]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypoalbuminemia		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Erythroderma		
Pruritus			***Pruritus (Gr 2)***
Rash[2]			***Rash[2] (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]Rash includes the terms: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, erythema, rash follicular, dermatitis, dermatitis contact.

Adverse events reported on ensartinib (X-396 hydrochloride) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ensartinib (X-396 hydrochloride) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy); Eosinophilia; Leukocytosis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (sinus arrhythmia); Chest pain - cardiac; Conduction disorder; Palpitations; Pericardial effusion; Pericarditis; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - External ear pain; Tinnitus
ENDOCRINE DISORDERS - Testosterone deficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (diplopia); Eye disorders - Other (eye pruritus); Eye disorders - Other (eye swelling); Eye disorders - Other (eyelid edema); Eye disorders - Other (eyelid pruritus); Eye disorders - Other (ocular hyperemia); Eye pain; Flashing lights; Floaters; Periorbital edema; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Belching; Dry mouth; Dyspepsia; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (lip dry); Gastrointestinal disorders - Other (salivary hypersecretion); Oral pain; Periodontal disease

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (hyperthermia); General disorders and administration site conditions - Other (nodule); General disorders and administration site conditions - Other (temperature intolerance); Generalized edema; Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (liver injury)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INFECTIONS AND INFESTATIONS - Conjunctivitis; Folliculitis; Fungemia; Lung infection; Otitis media; Paronychia; Pharyngitis; Rash pustular; Shingles; Sinusitis; Skin infection; Upper respiratory infection; Urinary tract infection; Viremia
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (nail bed bleeding); Injury, poisoning and procedural complications - Other (sunburn); Wound complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood lactate dehydrogenase increased; Blood prolactin abnormal; Cardiac troponin I increased; Cholesterol high; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Hemoglobin increased; Investigations - Other (alpha hydroxybutyrate dehydrogenase increased); Investigations - Other (blood chloride increased); Investigations - Other (blood fibrinogen increased); Investigations - Other (blood follicle stimulating hormone increased); Investigations - Other (blood luteinizing hormone decreased); Investigations - Other (blood luteinizing hormone increased); Investigations - Other (blood urea increased); Investigations - Other (c-reactive protein increased); Investigations - Other (creatinine renal clearance); Investigations - Other (electrocardiogram high voltage); Investigations - Other (estradiol decreased); Investigations - Other (estradiol increased); Investigations - Other (fibrin D dimer increased); Investigations - Other (gamma-glutamyltransferase decreased); Investigations - Other (monocyte count increased); Investigations - Other (nitrite urine present); Investigations - Other (platelet count increased); Investigations - Other (progesterone decreased); Investigations - Other (progesterone increased); Investigations - Other (protein total decreased); Investigations - Other (thrombin time prolonged); Investigations - Other (total bile acids increased); Investigations - Other (urobilinogen urine increased); Investigations - Other (white blood cells urine positive); Lipase increased; Lymphocyte count decreased; Lymphocyte count increased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Urine output decreased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hyperlipidemia; Hypermagnesemia; Hyperphosphatemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypochloremia); Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (hypouricemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (mastication disorder); Musculoskeletal and connective tissue disorder - Other (muscle atrophy); Myalgia; Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Skin papilloma
NERVOUS SYSTEM DISORDERS - Anosmia; Dizziness; Dysesthesia; Dysphasia; Edema cerebral; Headache; Nervous system disorders - Other (osmotic demyelination syndrome); Nervous system disorders - Other (poor quality sleep); Nervous system disorders - Other (visual field defect); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Anxiety; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Dysuria; Glucosuria; Hematuria; Proteinuria; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Reproductive system and breast disorders - Other (vulvovaginal erythema)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Respiratory, thoracic and mediastinal disorders - Other (nasal dryness); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Eczema; Erythema multiforme; Hyperhidrosis; Nail changes; Nail discoloration; Nail loss; Nail ridging; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (drug eruption); Skin and subcutaneous tissue disorders - Other (drug rash with eosinophilia & systemic symptoms); Skin and subcutaneous tissue disorders - Other (lichenoid keratosis); Skin and subcutaneous tissue disorders - Other (scab); Skin and subcutaneous tissue disorders - Other (skin discoloration); Skin and subcutaneous tissue disorders - Other (skin fissures); Skin and subcutaneous tissue disorders - Other (skin fragility); Skin and subcutaneous tissue disorders - Other (skin irritation); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin and subcutaneous tissue disorders - Other (skin mass); Skin atrophy; Skin hyperpigmentation; Skin ulceration; Telangiectasia; Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (jugular vein distension)

Note: Ensartinib (X-396 hydrochloride) 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.

7.3.6 Lorlatinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Lorlatinib (PF-06463922, NSC 803411)

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 822 patients.* Below is the CAEPR for Lorlatinib (PF-06463922).

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 2.3, September 1, 2021[1]

Adverse Events with Possible Relationship to Lorlatinib (PF-06463922) (CTCAE 5.0 Term) [n= 822]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Atrioventricular block complete	
		Atrioventricular block first degree	
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 2)***
		Pancreatitis	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema limbs			***Edema limbs (Gr 2)***
	Fatigue		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
Cholesterol high			***Cholesterol high (Gr 2)***
	Lipase increased		
	Weight gain		***Weight gain (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
		Hyperglycemia	
		Hyperlipidemia	

Adverse Events with Possible Relationship to Lorlatinib (PF-06463922) (CTCAE 5.0 Term) [n= 822]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Hypertriglyceridemia			***Hypertriglyceridemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
NERVOUS SYSTEM DISORDERS			
		Central nervous system necrosis	
	Cognitive disturbance		***Cognitive disturbance (Gr 2)***
	Memory impairment		
	Paresthesia		***Paresthesia (Gr 2)***
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
	Peripheral sensory neuropathy		***Peripheral sensory neuropathy (Gr 2)***
		Seizure	
PSYCHIATRIC DISORDERS			
		Hallucinations	
	Psychiatric disorders - Other (affect lability/mood altered/mood swings)		
		Suicidal ideation	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
VASCULAR DISORDERS			
		Hypertension	

[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.

Adverse events reported on lorlatinib (PF-06463922) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lorlatinib (PF-06463922) caused the adverse event:

CARDIAC DISORDERS - Cardiac disorders - Other (cardiac tamponade); - Cardiac disorders -

Other (left ventricular dysfunction); Chest pain - cardiac; Heart failure; Palpitations; Pericardial effusion; Sinus bradycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (diplopia); Flashing lights; Floaters; Photophobia; Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal distension; Constipation; Dry mouth; Gastritis; Gastroesophageal reflux disease; Mucositis oral; Nausea; Small intestinal obstruction; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Generalized edema
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic function abnormal)
INFECTIONS AND INFESTATIONS - Lung infection; Skin infection; Wound infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (traumatic intracranial hemorrhage, intentional self-injury)
INVESTIGATIONS - Alkaline phosphatase increased; CPK increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Anorexia; Hyperkalemia; Hyperuricemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Myalgia; Myositis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (neoplasm progression, pericardial effusion malignant)
NERVOUS SYSTEM DISORDERS - Amnesia; Concentration impairment; Dizziness; Dysarthria; Dysesthesia; Dysgeusia; Dysphasia; Intracranial hemorrhage; Ischemia cerebrovascular; Headache; Nervous system disorders - Other (neurological symptom, carpal tunnel syndrome); Neuralgia; Presyncope; Stroke; Vagus nerve disorder
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Delirium; Depression; Euphoria; Insomnia; Irritability; Personality change; Psychiatric disorders - Other (mental status changes); Psychiatric disorders - Other (schizophreniform disorder)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Respiratory failure; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
SURGICAL AND MEDICAL PROCEDURES - Surgical and medical procedures - Other (radiotherapy to bone)
VASCULAR DISORDERS - Thromboembolic event; Vascular disorders - Other (thrombosis)

Note: Lorlatinib (PF-06463922) 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.

7.3.7 Pemetrexed: Below is a list of most common adverse events. Refer to the approved package insert for a list of comprehensive adverse events.

- Tiredness
- Nausea
- Loss of appetite

7.3.8 Cisplatin: Below is a list of most common adverse events. Refer to the approved package insert for a list of comprehensive adverse events.

- Joint pain
- Loss of balance
- Ringing in ears
- Swelling of feet or lower legs
- Trouble in hearing
- Unusual tiredness or weakness
- Nausea and vomiting

7.3.9 Carboplatin: Below is a list of most common adverse events. Refer to the approved package insert for a list of comprehensive adverse events.

- Pain at place of injection
- Nausea and vomiting
- Unusual tiredness and weakness

7.4 Expedited Reporting of Adverse Events (20-May-2019)

All adverse events (AEs) are submitted for expedited reporting protocol-specific rules evaluation using the Medidata Rave data management system. All AEs will be evaluated by the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) to determine whether expedited reporting is recommended based on a set of programmed expedited reporting rules. AEs identified as meeting the programmed expedited reporting requirements can then be submitted in CTEP-AERS. A deep link in Rave will take the user directly to CTEP-AERS where the expedited report may be completed and submitted via CTEP-AERS.

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the link in RAVE. CTEP-AERS is also accessed via the CTEP web site, but all expedited reports must be initiated in RAVE , https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology by phone at 1-215-574-3191 and the NCI (301-897-7497). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event ..
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact NRG Oncology at 1-215-574-3191 for details to submit source documentation (CTEP fax: 301-230-0159.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements for Adverse Events

Late Phase 2 and Phase 3 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 CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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 reported via CTEP-AERS 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 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 4, and Grade 5 AEs **Expedited 10 calendar day reports for:** • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events [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

7.4.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.4.4 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 during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported 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.

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.

7.4.5 Pregnancy

Investigators should report a pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test, including a male participant's impregnation of his partner, expeditiously

as a grade 3 SAE coded in the CTCAE v.5.0 as "pregnancy, puerperium and perinatal conditions, other—pregnancy" in CTEP-AERS and submit the Pregnancy Report Form in Rave within 14 days of notification.

Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant, including a male participant's impregnation of his partner. The pregnancy outcome for patients on study should be reported to NRG.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (20-MAY-2019)

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 at 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, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their

practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, must be rostered at the enrolling site with a participating organization.

Additional information is located 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.

8.1 CTSU Registration Procedures (20-JAN-2022)

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/ Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-LU003 Site Registration
Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-LU003;*
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website,go to the Regulatory section and select Regulatory Submission.

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

Checking Your Site's Registration Status:
Site registration status may be verified on the CTSU members' website.

-
- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. 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.

8.2 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.2.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk 215-574-3191 Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

8.3 Digital Data Submission of Images to NRG Using TRIAD (11-AUG-2020)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-

Support@acr.org or 1-703-390-9858.

9.0 DRUG INFORMATION

9.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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. 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, a "current" password, and active person registration status. 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.

9.1.1 Starter supplies are not being provided. Patients must be registered in Step 2 prior to sites ordering study agents.
Refer to the Policy and Guidelines for Investigational Agent Ordering and the contact information below for order processing time and conditions. Normal order processing time is two business days. An express courier account number must be provided for next-day delivery.

CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm

PMB Online Agent Order Processing (OAOP) application:
https://ctepcore.nci.nih.gov/OAOP/
CTEP Identity and Access Management (IAM) account:
https://ctepcore.nci.nih.gov/iam/
CTEP 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)

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.

9.1.2 To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure (IB), if available, for comprehensive pharmacologic and safety information. The current version of the Investigator Brochure (IB) 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, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email to ibcoordinator@mail.nih.gov or the IB Coordinator may be contacted at 240-276-6575.

9.2 Investigational Study Agent: Alectinib ([redacted], NSC #794611) (13-NOV-2019)
Sites must refer to the Investigator Brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See section 9.1.2.

Chemical Name: 9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile hydrochloride

Other Names: RO5424802, CH5424802, ALECENSA®

Classification: tyrosine kinase inhibitor

Molecular Formula: C30H35ClN4O2 (hydrochloride salt)

M.W.: 519.08 g/mol (hydrochloride salt); 482.62 g/mol (free base form)

Mode of Action: tyrosine kinase inhibitor targeting ALK and RET

Description: Alectinib hydrochloride is a white to yellow reddish white powder or powder with lumps.

How Supplied: Genentech supplies and CTEP, DCTD, NCI distributes alectinib as white colored, hard capsules containing 150 mg of alectinib as the free base (equivalent to 161.3 mg of alectinib HCl) and the following inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, and carboxymethylcellulose calcium. The capsule shell is composed of hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. "ALE 150 mg" is printed on the capsules with black ink. The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate. Each bottle contains 240 capsules.

Storage: Do not store above 30°C. Store in original container to protect from light and

moisture.

If a storage temperature excursion is identified, promptly return alectinib to Controlled Room Temperature (CRT) 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: Refer to the package label for expiration. Dispense in the original container.

Route of Administration: Oral

Method of Administration: Alectinib must be taken with food for optimal absorption. Capsules should be swallowed whole. Do not open or dissolve the contents of the capsule.

Potential Drug Interactions: In vitro studies indicate that neither alectinib nor its major metabolite (M4) inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib is a competitive inhibitor of CYP2C8. Alectinib and M4 showed a weak time-dependent inhibition of CYP3A4. However, the coadministration of alectinib did not affect the pharmacokinetics of CYP3A and CYP2C8 sensitive substrates. Alectinib also has the potential for moderate induction of CYP3A4 and CYP2B6 at clinical concentrations. Systemic exposure to alectinib was not affected when co-administered with a strong CYP3A inhibitor or inducer.

Alectinib is not a substrate of the efflux transporters P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), whereas M4 is a substrate of P-gp but not of BCRP. Alectinib and M4 are inhibitors of P-gp and BCRP. Appropriate monitoring is recommended when administering alectinib with P-gp or BCRP substrates.. Alectinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transport activity in vitro.

The co-administration of PPIs and other agents that raise gastric pH have no clinically relevant impact on alectinib pharmacokinetics.

Patient Care Implications: An extra dose should not be taken if a patient misses a dose or vomits after taking a dose. The next dose should be taken at the next regular scheduled time.

Females of reproductive potential must use effective contraception during treatment and for a minimum of one (1) week after the final dose. Males with female partners of reproductive potential must use effective contraception during treatment and for a minimum of three (3) months following the final dose.

9.2.1 Subjects must be enrolled and assigned to the alectinib treatment arm prior to submitting the agent request to PMB. See section 9.1.1

9.2.2 Availability/Supply

Alectinib capsules are provided by Genentech and distributed by the DCTD/NCI.

Alectinib will be supplied to patients on study free of charge.

9.3 Investigational Study Agent: Brigatinib [redacted], NSC #784728)

Sites must refer to the Investigator Brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See section 9.1.2.

Chemical Name or Amino Acid Sequence: 5-chloro-N4-[2-(dimethylphosphoryl)phenyl]-N2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2, 4-diamine

Other Names: AP26113

Classification: anaplastic lymphoma kinase (ALK) inhibitor

CAS Registry Number: 1197953-54-0

Molecular Formula: C29H39ClN7O2P **M.W.:** 584.10 g/mol

Approximate Solubility: pH dependent (>165.2 mg/ml at pH 2.5, >355.2 mg/mL at pH 4.5, 3 mg/ml at pH 7)

Mode of Action: Brigatinib is an oral tyrosine kinase inhibitor (TKI) targeting activated variants of ALK including the L1196M gatekeeper mutation and c-ros oncogene 1 (ROS1) kinase. It also inhibits certain variants of epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor 1 (IGF-1R).

How Supplied: Brigatinib is supplied by Takeda Pharmaceuticals and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Brigatinib is available as 30 mg film coated tablets packaged in 60-count HDPE bottles. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydrophobic colloidal silica, and magnesium stearate. The tablet film-coating is comprised of talc, propylene glycol, polyvinyl alcohol, and titanium dioxide.

Storage: Store at controlled room temperature 20°C – 25°C. Excursions permitted between 15°C – 30°C.

If a storage temperature excursion is identified, promptly return brigatinib to below 30°C 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: Stability studies are ongoing. Dispense in the original container.

Route and Method of Administration: Oral with or without food. Swallow whole, do not crush.

Potential Drug Interactions: Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 in vitro, and a minor extent by CYP3A5. It is also a substrate of P-gp, BCRP, and OATP1A2 but not OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2K, BSEP, or NTCP. P-gp, BCRP, and OATP1A2 inhibitors are unlikely to increase the plasma concentration of brigatinib due to high solubility and permeability in vitro. In vivo, CYP2C8 does not appear to contribute meaningfully to clearance of brigatinib. Strong inhibitors and inducers of CYP3A4 should be avoided. Strong inhibitors and inducers of CYP2C8 should be used with caution.

Brigatinib inhibits P-gp, BCRP, MATE1, MATE2K, and OCT1 in vitro. Brigatinib and its metabolite AP26123 do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant drug concentrations in vitro. Brigatinib also did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP. Use caution when administered with agents that are P-gp, BCRP, OCT1, MATE1, and MATE2K substrates.

Brigatinib induces CYP3A and 2C enzymes through activation of the pregnane X receptor (PXR) and is a weak inducer of CYP1A2 and 2B6. Use caution when administered with agents that are CYP3A or 2C substrates.

Patient Care Implications: Females of childbearing potential should use effective contraception during treatment with brigatinib and for at least 4 months after the last dose of brigatinib. A non-hormonal method of contraception should be used as brigatinib can render some hormonal contraceptives ineffective. Males with female partners of reproductive potential should use effective contraception during treatment with brigatinib and for at least 3 months after the last dose of brigatinib. Lactating women should not breastfeed their children during treatment with brigatinib and for 1 week following the last dose.

9.3.1 Subjects must be enrolled and assigned to the brigatinib treatment arm prior to submitting the agent request to PMB. See section 9.1.1

9.3.2 Availability/Supply

Brigatinib tablets are provided by Ariad Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and distributed by the DCTD/NCI. Brigatinib will be supplied to patients on study free of charge.

9.4 Investigational Study Agent: LDK378 (ceritinib) ([redacted] NSC #802646) (13-NOV-2019)

Sites must refer to the investigator brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See section 9.1.2.

Chemical Name: 5-Chloro-2-N-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2-yl)oxy]phenyl}-4-N-[2-(propane-2-sulfonyl)phenyl]pyrimidine-2,4-diamine

Other names: LDK378-NXA, Zykadia®

Classification: anaplastic lymphoma kinase (ALK) inhibitor

Molecular Formula: C28H36N5O3ClS **M.W.:** 558.14 (free base)

Approximate Solubility: The 150 capsule is completely soluble in 250 mL of acidic media (pH=1) and much less soluble in 250 mL of neutral media (0.05 mg at pH=6.8).
Mode of Action: ALK is a receptor tyrosine kinase linked to the genesis of several cancers through genetic aberrations involving translocation of the kinase domain with multiple fusion partners or activating mutations that result in ligand-independent constitutive activation. LDK378 (ceritinib) is an oral, highly selective and potent ALK kinase inhibitor which inhibits autophosphorylation of ALK, and consequently ALK-mediated phosphorylation of downstream signaling proteins and proliferation of ALK-dependent cancer cells.

How Supplied: Novartis supplies and the Pharmaceutical Management Branch, CTEP, DCTD, NCI distributes LDK378 (ceritinib) as 150 mg hard gelatin capsules (HGC). Capsules are contained in 35-count HDPE bottles with induction seals.

LDK378 (ceritinib) capsules contain drug substance, cellulose, microcrystalline/microcrystalline cellulose:low-substituted hydroxypropyl cellulose, magnesium stearate, sodium starch glycolate (type A)/sodium starch glycolate, silica and colloidal anhydrous/colloidal silicon dioxide. Capsule shells contain the following: gelatin; titanium dioxide (E171); indigotine (E132)/FD&C Blue No. 2 (for blue-white capsules).

LDK378 (ceritinib) 150 mg capsules are white opaque size #00 HGC with a blue opaque cap. Capsules are marked with “LDK 150MG” on the cap and “NVR” on the body in a black radial rectified imprint. Printing ink contains the following components: ammonium hydroxide 28%; iron oxide black (E172)/ferric oxide, black; propylene glycol; and shellac (bleached, de-waxed) glaze 45%.

Storage: Store below 25°C (77°F).
If a storage temperature excursion is identified, promptly return LDK378 (ceritinib) to below 25°C (77°F) 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: Stability studies are ongoing. Dispense in the original container.

Route and Method of Administration: Oral. Take LDK378 (ceritinib) once daily with food. Swallow LDK (ceritinib) capsules whole and without chewing or crushing.

If a dose of LDK378 (ceritinib) is missed, make up that dose unless the next dose is due

within 12 hours. If vomiting occurs during the course of treatment, do not administer an additional dose and continue with the next scheduled dose of LDK378 (ceritinib).

Potential Drug Interactions: Based on clinical data, CYP3A4/5 was the major enzyme responsible for metabolic clearance of LDK378 (ceritinib). Strong CYP3A4/5 inhibitors increased the systemic exposure of LDK378 (ceritinib) and strong inducers decreased systemic exposure of LDK378 (ceritinib). If concomitant use of strong CYP3A4/5 inhibitors or inducers is unavoidable, refer to the protocol document for LDK378 (ceritinib) dose adjustments. Patients should avoid ingesting grapefruit or grapefruit juice since inhibition of CYP3A4/5 in the gut wall may increase the bioavailability of LDK378 (ceritinib).

Based on *in vitro* data, LDK378 (ceritinib) is a substrate of the efflux transporter P-glycoprotein (P-gp), but not BCRP, MRP2, OCT1, OCT2, OAT2 or OATP1B1. Exercise caution with concomitant use of P-gp inhibitors and inducers and carefully monitor adverse drug reactions.

LDK378 (ceritinib) may inhibit CYP3A and CYP2C9 at clinical concentrations. Avoid concurrent use of CYP3A and CYP2C9 substrates known to have narrow therapeutic indices or substrates primarily metabolized by CYP3A and CYP2C9 during treatment with LDK378 (ceritinib).

In vitro studies show that LDK378 (ceritinib) does not inhibit transporters BCRP, P-gp or MRP2 at pH of 7.4 or OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2 or OAT3. Follow-up *in vitro* studies at pH 6.0 show that LDK378 (ceritinib) inhibits intestinal P-gp and BCRP, but not MRP2. LDK378 (ceritinib) also inhibits MATE-1, but not MATE2-K, suggesting that LDK378 (ceritinib) could lead to increased serum creatinine elevations by blocking *in vivo* clearance.

Co-administration of LDK378 (ceritinib) and proton pump inhibitors showed a decrease in AUC and Cmax. Further subgroup analysis across multiple trials showed similar steady-state exposure of LDK378 (ceritinib) in patients with and without proton pump inhibitors.

Since LDK378 (ceritinib) may increase the exposure of drugs which are metabolized via CYP3A4/5, avoid concomitant administration with QTc prolonging medications which are metabolized by CYP3A4/5. Refer to the protocol document for dose adjustments and management of QT prolongation. Avoid co-administration with other agents known to cause bradycardia.

Patient Care Implications: Women should not breastfeed during treatment and for 2 weeks following completion of therapy. Advise females of reproductive potential to use effective contraception during treatment with LDK378 (ceritinib) and for 6 months following completion of therapy. Advise males with female partners of reproductive potential to use condoms during treatment with LDK378 (ceritinib) and for 3 months following completion of therapy. Refer to the protocol document for further details.

9.4.1 Subjects must be enrolled and assigned to the LDK378 (ceritinib) treatment arm prior to submitting the agent request to PMB. See section 9.1.1

9.4.2 Availability/Supply
LDK378 (ceritinib) capsules are provided by Novartis and distributed by the DCTD/NCI. LDK378 (certinib) will be supplied to patients on study free of charge.

9.5 Investigational Study Agent: Crizotinib ([redacted], NSC #749005) (13-NOV-2019)
Sites must refer to the investigator brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See section 9.1.2.

Chemical Name: (*R*)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1*H*-pyrazol-4-yl)-pyridin-2-ylamine

Other Names: Xalkori®, PF-02341066

Classification: ALK inhibitor

CAS Registry Number: 8773999-52-5

Molecular Formula: C21H22Cl2FN5O **M.W.:** 450.34 daltons

Mode of Action: Crizotinib is a selective ATP-competitive small –molecule inhibitor of anaplastic lymphoma kinase (ALK), c-Met/hepatocyte growth factor receptor (HGFR) and Recepteur d'Origine Nantais (RON), and ROS1 receptor tyrosine kinases and their oncogenic variants. Translocations of these genes can result in expression of oncogenic fusion proteins that contribute to increased cell proliferation and survival. Antitumor efficacy of crizotinib is correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion variants or c-Met/HGFR in tumors i*n vivo*.

Description: white to pale yellow powder

How Supplied: Crizotinib capsules are supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Capsules are packaged in 60-count bottles with colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, and magnesium stearate as inactive ingredients in the following strengths:

- 200 mg hard gelatin capsule (size 1) white opaque body and pink opaque cap, with "Pfizer" on the cap and "CRZ 200" on the body.
- 250 mg hard gelatin capsule (size 0) pink opaque cap and body, with "Pfizer" on the cap and "CRZ 250" on the body.

The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin, and titanium dioxide.

The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

Storage: Store at room temperature 20° to 25°C (68° to 77°F), excursions permitted between 15 to 30°C (59 to 85°F).

If a storage temperature excursion is identified, promptly return crizotinib to between 15 and 30°C 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: Refer to the package label for expiration. Dispense in the original container.

Route of Administration: Take by mouth with or without food.

Potential Drug Interactions: Crizotinib is primarily metabolized by CYP 3A4/5 with minor contributions from CYP2C8, CYP2C19, and CYP2D6. Avoid concomitant use of strong CYP3A inhibitors and inducers. Use of potent CYP3A inducers should be avoided for at least 12 days prior to the first dose of crizotinib. Use of strong CYP3A inhibitors should be avoided for at least 7 days prior to the first dose of crizotinib. Exercise caution with concomitant use of moderate CYP3A inhibitors. Crizotinib moderately inhibits CYP3A4 in a time-dependent fashion. Avoid use with patients who receive CYP3A4 substrates with a narrow therapeutic index.

Crizotinib is an inhibitor of CYP2B6 in vitro. Use caution with co-administered drugs that are predominantly metabolized by CYP2B6.

Studies demonstrate that crizotinib is a substrate of P-gp and a weak BCRP inhibitor, however the potential to cause drug-drug interactions at therapeutic doses is low. Crizotinib inhibited P-gp, OCT1, and OCT2 in vitro at clinically relevant concentrations. Use caution with coadministration of P-gp, OCT1, and OCT2 substrates.

Patient Care Implications: Females of childbearing potential must use adequate contraception for 90 days after the last dose of crizotinib.

9.5.1 Subjects must be enrolled and assigned to the crizotinib treatment arm prior to submitting the agent request to PMB. See section 9.1.1

9.5.2 Availability/Supply

Crizotinib capsules are provided by Pfizer Pharma and distributed by the DCTD/NCI Crizotinib will be supplied to patients on study free of charge.

9.6 Investigational Study Agent: Ensartinib ([redacted], NSC #784729) (13-NOV-2019)

Sites must refer to the investigator brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See section 9.1.2.

Chemical Name or Amino Acid Sequence: 6-amino-5-(R)-(2,6-dichloro-3-fluorophenyl)ethoxy-N-(4-(3R,5S)-3,5-dimethylpiperazine-1-carbonyl)phenyl)pyridazine-3-carboxamide HCl salt

Other Names: X0396, X-0396, X396

Classification: anaplastic lymphoma kinase (ALK) inhibitor

Molecular Formula: $C_{26}H_{27}Cl_2FN_6O_3$ *2HCl **M.W.:** 634.4 (HCl salt) 561.4 (free base)

Approximate Solubility: pH and solvent dependent [(27.5 mg/mL in purified water, 8.2 mg/ml at pH 1.2 (simulated gastric fluid without enzymes)]

Mode of Action: A potent and selective 2nd generation ALK inhibitor with additional activity against MET, ABL T315I, Ax1, EPHA2, and ROS1. ALK translocations can result in increased cell proliferation and survival. Ensartinib inhibits cell growth and ALK receptor phosphorylation.

Description: White to off-white solid. Ensartinib (X-396 HCl) is hygroscopic.

How Supplied: Xcovery Holding Company, LLC supplies and CTEP, DCTD, NCI distributes ensartinib (X-396 HCl) as 25 mg capsules (white opaque, size 2) and 100 mg capsules (yellow opaque body with blue opaque cap, size 0). Inactive components consist of microcrystalline cellulose and stearic acid. The capsules are packaged in 40 cc (25 mg) and 60 cc (100 mg) HDPE bottles containing 30 capsules per bottle with a desiccant, induction seal, and child resistant screw cap.

Storage: Stored at controlled room temperature (15ºC-30ºC/59ºF-86ºF)

If a storage temperature excursion is identified, promptly return ensartinib to controlled room temperature 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: Stability studies are ongoing. Dispense in the original container.

Route and Method of Administration: Oral with or without food.

Potential Drug Interactions: Ensartinib is primarily metabolized by CYP3A4 with a minor contribution from 2C19 in vitro. Use caution when administered with strong inhibitors and inducers of CYP3A4.

In vitro, ensartinib did not inhibit cytochrome P450 isozymes CYP 1A2 or 2D6 but did inhibit 3A4 by 22% and 2C9 by 43% at 10 μM. While drug-drug interactions via cytochrome P450 isozymes are not expected at concentrations achieved in the clinic,

substrates of CYP3A4 and 2C9 should be used with caution.

Plasma protein binding ranged from 90.2% to 97%. Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

Patient Care Implications: Females of childbearing potential and male participants with female partners should use adequate contraception for at least 1 week after the last dose of ensartinib.

9.6.1 Subjects must be enrolled and assigned to the ensartinib treatment arm prior to submitting the agent request to PMB. See section 9.1.1

9.6.2 Availability/Supply
Ensartinib capsules are provided by Xcovery Pharma and distributed by the DCTD/NCI. Ensartinib will be supplied to patients on study free of charge.

9.7 Investigational Study Agent: Lorlatinib ([redacted], NSC #803411) (11-AUG-2020)
Sites must refer to the investigator brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See section 9.1.2.

Chemical Name: (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile

Other Names: Lorbrena®, PF-06463922

Classification: ALK inhibitor

Molecular Formula: $C_{21}H_{19}FN_6O_2$ **M.W.:** 406.41 daltons

Mode of Action: Lorlatinib is a selective ATP-competitive small –molecule inhibitor of anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1) kinase that also potently inhibits ALK kinase domain mutations responsible for resistance to ALK inhibitor treatment in non-small cell lung cancer. Lorlatinib is able to cross the blood brain barrier.

Description: The lorlatinib drug substance is a white to off-white powder.

How Supplied: Lorlatinib is supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Tablets contain drug substance, microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate. Tablets are packaged in 30-count bottles in the following strengths:

- 25 mg tablet: 8 mm round, tan, immediate release film-coated, debossed with “Pfizer” on one side and “25” and “LLN” on the other side

- 100 mg tablet: 8.5 mm × 17 mm oval, lavender, immediate release, film-coated, debossed with "Pfizer" on one side and "LLN 100" on the other side

The film-coating contains hydroxypropyl methylcellulose (HPMC) 2910/hypromellose, lactose monohydrate, macrogol/polyethylene glycol (PEG) 3350, triacetin, titanium dioxide, ferrosoferric oxide/black iron oxide, and iron oxide red.

Storage: Store at room temperature 20° to 25°C (68° to 77°F), excursions permitted between 15 to 30°C (59 to 85°F).

If a storage temperature excursion is identified, promptly return lorlatinib to between 15 and 30°C 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: Refer to the package label for expiration. Dispense in the original container.

Route of Administration: Oral administration. May be administered without regard to food.

Potential Drug Interactions: Lorlatinib is primarily metabolized by CYP3A4 and UGT1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, CYP1A2, and UGT1A3. Avoid concomitant use of strong CYP3A4/5 inhibitors and strong to moderate CYP3A4/5 inducers. Exercise caution with concomitant use of moderate CYP3A4/5 inhibitors. Lorlatinib is a time-dependent inhibitor as well as inducer of CYP3A4/5. Avoid concomitant use of CYP3A4/5 substrates with a narrow therapeutic index. Lorlatinib is a weak inducer of CYP2B6, CYP2C9, and UGT isoforms. Use caution with coadministration of CYP2B6, CYP2C9, and UGT substrates. Lorlatinib is a moderate inducer of P-gp. Coadministration of lorlatinib with P-gp substrates with narrow therapeutic indices should be avoided.

Lorlatinib may have the potential to inhibit P-gp, BCRP, OCT1, MATE1, OATP1B1, OATP1B3, and OAT3. In vitro studies indicate that clinical interactions with substrates of these transporters are unlikely to occur.

Patient Care Implications: Females of childbearing potential and partners of patients during treatment must use adequate contraception during treatment and for a minimum of 3 months after the last dose of lorlatinib.

9.7.1 Subjects must be enrolled and assigned to the lorlatinib treatment arm prior to submitting the agent request to PMB. See section 9.1.1

9.7.2 Availability/Supply

Lorlatinib tablets are provided by Pfizer Pharma and distributed by the DCTD/NCI. Lorlatinib will be supplied to patients on study free of charge.

9.8 Commercial Agent: Pemetrexed (NSC# 698037)

9.8.1 Product Description

Dosage Form: 50mg or 100mg as a white to light-yellow or green-yellow lypholized powder in single-dose vials for reconstitution for intravenous infusion.
Active ingredient: pemetrexed
Inactive ingredients: mannitol, hydrochloric acid and/or sodium hydroxide may be added to adjust pH.
Packaging: carton containing one single-dose vial of 50mg or 100mg pemetrexed

9.8.2 Availability/Supply

Drug will be supplied commercially. Please see Section 5.2 for administration instructions. Please refer to the current FDA approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling and storage.

Patient Care Implications: Females of childbearing potential must use adequate contraception for 6 months during treatment and after the last dose. Males with female partners must use adequate contraception during treatment and for 3 months after the last dose.

9.9 Commercial Agent: Cisplatin (NSC# 119875)

9.9.1 Product Description

Dosage Form: Intravenous infusion; intravenous powder for solution
Active ingredient: cisplatin
Inactive ingredients: sodium chloride, hydrochloric acid, sodium hydroxide, water
Packaging: 50mL or 100mL per vial

9.9.2 Availability/Supply

Drug will be supplied commercially. Please see Section 5.2 for administration instructions. Please refer to the current FDA approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling and storage.

Patient Care Implications: Females of childbearing potential must use adequate contraception during treatment and for 6 months after the last dose. Male patients must use highly effective contraception for a total of 6 months after last dose of chemotherapy.

9.10 Commercial Agent: Carboplatin (NSC# 241240)

9.10.1 Product Description

Dosage Form: Intravenous infusion; intravenous powder for solution
Active ingredient: carboplatin
Inactive ingredients: mannitol, water
Packaging: Injectable solution is packaged in vials of 50, 150, 450 and 600mg.

9.10.2 Availability/Supply

Drug will be supplied commercially. Please see Section 5.2 for administration

instructions. Please refer to the current FDA approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling and storage.

Patient Care Implications: Females of childbearing potential must use adequate contraception during treatment and for 6 months after the last dose. Male patients must use highly effective contraception for a total of 6 months after last dose of chemotherapy.

10. PATHOLOGY/BIOSPECIMEN (17-FEB-2020)

10.1 Mandatory Central Pathology Review for Integrated Marker Testing (17-FEB-2020)

10.1.1 Prospective Review: Submission of tissue and blood to Foundation Medicine after patient enrollment is mandatory for all patients.

- Foundation Medicine (FMI) performs pathology review on all samples received and analyzed as per standard quality control procedures. Please refer to Appendices I-IV for guidelines around appropriate tissue preparation and specifications around FoundationOne®CDx and FoundationOne®Liquid testing.
- For all samples tested at Foundation Medicine, pathology review is included in the average turn-around-time of 14 calendar days from time of sample receipt to sample reporting.
- Standard Foundation Medicine testing requires the submission of a complete pathology report for each patient. Foundation Medicine will perform an initial pathology review of all submitted samples to confirm appropriate disease ontology classification.
  - Any discrepancies between Foundation Medicine pathology review and diagnosis noted on the original pathology report will be immediately communicated to the ordering provider. The final report diagnosis is at the discretion of the ordering provider and their pathologist.
- Special Foundation Medicine FFPE and Blood Kits with prepaid labels can be requested from the Foundation Medicine (clinical.operations@foundationmedicine.com)

10.1.2 Please refer to Section 15 for markers to be tested and their usage.

10.1.3 Testing requirements and reporting:

- Samples should be shipped in kit provided by Foundation Medicine. H&E Slide and block or H&E slide and 10 unstained slides (5 microns thick). See Appendix II for further details.
- Blood samples collected in special tubes, in the kit provided by Foundation Medicine (See Appendix IV)
- Samples must be sent to Foundation Medicine after the patient is enrolled to NRG-LU003.
- All testing will be performed in a CLIA-certified and licensed testing facility, with results reported to NRG Oncology.
- NRG Oncology will then notify the enrolling institution they may proceed to step 2 registration.
- In the event that a patient experiences progression following study entry, the complete report from Foundation Medicine may be requested from NRG Oncology

Data Management (see cover page for contact information).

10.1.4 Testing must be completed within 14-21 days upon receipt. Method of testing: [e.g., IHC, RT-PCR, FISH, etc.]

- FoundationOne®CDx utilizes a hybrid-capture, next-generation sequencing testing method on solid tissue biopsies. For more information, please refer to the technical specifications as described in Appendix I.
- FoundationOne®Liquid utilizes a hybrid-capture, next-generation sequencing testing method on liquid (blood) biopsies. For more information, please refer to the technical specifications as described in Appendix III.
- Specimen requirements FoundationOne®CDx: please refer to the specimen preparation instructions as described in Appendix II.
- FoundationOne®Liquid : please refer to the specimen preparation instructions as described in Appendix IV.

- Test report range
  - Results from FoundationOne®CDx and FoundationOne®Liquid testing will specify genomic alterations, as listed in Table 1 of Section 15.1.
- Actionable values
  - FoundationOne®CDx: please refer to the performance specifications as described in Appendix I.
  - FoundationOne®Liquid : please refer to the performance specifications as described in Appendix III.
- Invalid test results: When testing cannot be performed within the validated parameters of a test, the result is an "invalid" result.

Failed Reports:

- If Foundation Medicine is unable to detect any genomic alterations in the specimen, either an alternate sample, if provided, will be tested, or a failed report will be generated.

Qualified Reports:

- In certain instances, Foundation Medicine does issue a Qualified Report which includes detected alterations but may reflect the potential of additional alterations that may have been detected had the specimen been of higher quality. Factors which may lead to a Qualified Report include the following: A second DNA signature: The presence of a second individual's DNA in the tested patient's specimen. The "contamination" can occur as a result of a past transplant procedure, or specimen mishandling by the outside institution. In cases where contamination is suspected, the ordering provider may be consulted to clarify transplant history.
- Gender discordance: Gender is confirmed as part of standard quality control metrics. The sex chromosome signals are expected to match the reported gender (e.g. if the patient is male, Foundation Medicine would expect to detect the Y chromosome in the subject's sample). If there is not a match, the ordering provider may be consulted to clarify the transplant history.
- Low coverage: If is specimen is of suboptimal quality, often the Foundation

Medicine laboratory will be unable to read over each part of the DNA sequence enough times for the assay's requirements. For FoundationOne®CDx, median coverage must be ≥ 250X or the report may be qualified. For FACT, median coverage must be ≥ 5000X.

- GC bias: With a suboptimal sample, there may be more GC nucleotide signals than AT signals. If the sample has been exposed to excessive heat while being embedded, is an older sample, or has been oxidized, an artificially higher signal level ("GC bias") can be created, which gives the impression of a copy number amplification when one is not actually present. This results in a reduced ability to detect low-level copy number amplifications.
- Low tumor purity: Tumor content is assessed by both the Foundation Medicine Pathology and Computational Biology teams. If the tumor purity is determined to be less than 20%, the ability to detect all present genomic alterations will be dramatically reduced.
- Low Reference Coverage: Two quality control samples are sequenced concurrent to test samples in order to confirm median coverage. If both control samples fail to report a median coverage of at least 250x, all samples on the plate would be considered unsuccessful.

- Location of testing
  FoundationOne®CDx and FoundationOne®Liquid testing will occur in a Foundation Medicine Laboratory. Samples should be shipped after the patient is enrolled to NRG-LU003 and with the NRG-LU003 patient identifier to:

  - Cambridge Accessioning
    Foundation Medicine, Inc
    150 Second Street
    Cambridge, MA 02141, USA

  - Contact Information:
    Email: clinical.operations@foundationmedicine.com
    Phone: 617.418.2200

10.1.5 Tissue Submission for testing: See Biospecimen Submission tables below in Section 10.2.

10.2 Biospecimen Submission Tables (17-FEB-2020)

10.2.1 Mandatory Specimen Submissions: Submission of tissue and blood to Foundation Medicine is mandatory after enrollment to NRG-LU003 for all patients.
See Appendix II and Appendix IV for Foundation medicine detailed specimen collection/processing/shipping instructions.

Mandatory Study Description #1 [for eligibility determination]

1) H&E slide and unstained slides are required to be submitted in a Foundation Medicine kit for central review for eligibility
2) Peripheral blood is required to be submitted in a Foundation Medicine Kit for blood analysis

3) Required Forms: Specimen Transmittal (SP) form, pathology report. All forms must be completely filled out with an NRG Label including the Study #, Case #, NRG Institution name and # or Institution NCI ID, and patient initials. The pathology accession number and date of procedure must remain visible on the pathology report but all other PHI information must be redacted/removed.
4) Kits: FFPE and Blood Kits should be requested from Foundation Medicine in advance of patient enrollment (clinical.operations@foundationmedicine.com)
5) Shipping costs: Fedex label will be provided in the Foundation Medicine kit for samples being shipped to Foundation Medicine. Foundation Medicine will incur cost of returns.
6) Results will be reported to NRG Oncology within 14 days of receipt of samples.
7) Residual Material:
    a. All residual material will be shipped to the NRGBB-San Francisco (NRGBB-SF) by Foundation Medicine following analysis. Samples will be banked for patients who consented to banking, or if requested by site, will be returned or destroyed.

Ship all biospecimens for mandatory central review in the Foundation Medicine kit for this trial to:
Cambridge Accessioning Foundation Medicine Inc
150 Second Street
Cambridge, MA 02141
clinical.operations@foundationmedicine.com
phone: 617.418.2200

Do **NOT** ship the required Foundation Medicine samples to the NRGBB, this will result in delays in central review testing.

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/Instructions for Site**	**Shipping** *See protocol-specific website for detailed specimen collection and shipment instructions*
FoundationOne®CDx FFPE Tissue: H&E Slide and Block (including core-needle biopsies, fine-needle aspirates, and effusion cytologies) or 10 unstained slides (4-5 microns thick) + 1 H&E slide	Prior to Step 1 registration	Please refer to Appendix II for Specimen Instructions	Ship by overnight using prepaid labels provided in kit. Refer to Appendix II for sample shipment information.
FoundationOne®Liquid Peripheral whole blood (two 8.5mL tubes)	Prior to Step 1 Registration and 30 days post-treatment (at progression)	Please refer to Appendix IV for Specimen Instructions	Ship Ambient with cold pack by overnight courier to Foundation Medicine using prepaid labels in kit: Tracking information must be sent day of shipment to clinical.operations@foundationmedicine.com

10.2.2 Optional Specimen Submissions

DO NOT Ship required Foundation Medicine kits to the NRGBB, please send required specimens to Foundation Medicine as per section 10.2.1 Only optional banking samples should be shipped to NRGBB-SF.

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

No studies will be conducted with the optional biospecimens without prior approval from CTEP. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

See detailed specimen collection/processing/shipping instructions on the protocol-specific website.

Specimen Collection for Banking for Future Research

Specimens are being collected for future translational research projects.

1) Required Forms: For FFPE samples: For patients that consented to banking an ST form and redacted pathology report must be also submitted to the NRGBB-SF at NRGBB@ucsf.edu or fax 415-476-5271. All forms must be completely filled out with an NRG Label including the Study #, Case #, NRG Institution name and # or Institution NCI ID, and patient initials. The pathology accession number and date of procedure must remain visible on the pathology report but all other PHI information must be redacted/removed.
2) Banking kits are available for frozen biospecimens from the NRGBB-SF. Sites should include the following information in their email: Sites ship to Fed Ex address with room number, confirm site has IRB approval for study, how many patients site enrolled in past month.
   Detailed Processing and shipping instructions are provided on the protocol-specific page of the CTSU website.
3) Shipping days for Frozen Specimens: Monday-Wednesday (U.S. sites). Check NRG Broadcasts for bank holiday closures. We are unable to accept shipments on Saturdays or holidays. Check Fed Ex site for storm delays and do not ship during severe weather.
4) Shipping costs: A single use prepaid Fed Ex label is included for banking samples from each case in LU003 kits provided to the site for batch shipping frozen biospecimens to the NRGBB-SF. Ship all Biospecimens for banking only to:

   NRG Oncology Biospecimen Bank – San Francisco
   2340 Sutter Street- Room S341
   UCSF
   San Francisco, CA 94115

415-476-7864/Fax 415-476-5271
Email: NRGBB@ucsf.edu

DO NOT Ship required Foundation Medicine kits to the NRGBB.

For questions about banking biospecimens contact:
NRG Oncology Biospecimen Bank – San Francisco
NRGBB@ucsf.edu
Phone: 415-476-7864/Fax 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
H&E slide(s) of Primary tumor and FFPE block or unstained slides	Pre-treatment and at progression	Forms: ST Forms, Pathology **Forms:** Copies of submission Forms and Pathology reports should be emailed to the NRGBB For patients that consented to banking- These pre-treatment samples will come from Foundation Medicine after testing is completed. The progression sample should be sent to NRGBB-San Francisco for banking.	Forms should be emailed/faxed to NRGBB@ucsf.edu / 415-476-5271 for all patients who consented to banking. The leftover pre-treatment tissue will be shipped from Foundation Medicine to NRGBB-San Francisco. Sites do not have to ship these to the NRGBB. Sites must ship the progression FFPE sample Ambient to NRGBB-San Francisco. Use of cold packs are encouraged during warm weather.
Whole Blood- one 5-10 ml EDTA tube	Cycle 3, Day 1 during treatment 30 days post treatment (+/- 3 days)	Collect blood, mix and aliquot 1-1.5 ml of whole blood per vial into three 2ml cryovials. Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice.	Ship on dry ice by overnight courier to NRGBB-San Francisco
Plasma- EDTA tube 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	At progression	Frozen plasma samples containing minimum **0.5 mL per aliquot** in 1 mL cryovials (five)	Plasma sent frozen in batch shipments on dry ice via overnight carrier to NRGBB-SF

11. MODALITY REVIEWS

The Medical Oncology study chairs will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 20 cases enrolled. The Medical Oncology study chairs will perform the next review after NRG Headquarters has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this study

has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

12. SPECIAL STUDIES (NON-TISSUE)

Not applicable for this protocol.

13. ASSESSMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 2 cycles Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

13.1.1 Definitions

Intracranial response

Intracranial response will be determined using modified RECIST 1.1 (Long et al, 2012)

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline and have begun protocol therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Measurable Disease

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

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

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

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 of the 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 or absence of unequivocal progression of each should be noted throughout follow-up.

13.1.2 Methods for Evaluation of 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 up to 4 weeks before step 2 registration.

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

Clinical Lesions

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

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 or less. If CT scans have slice thickness greater than 5 mm, 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 must 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.

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:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. 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.
3. 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.

13.2 Response Criteria

13.2.1 Evaluation of Target Lesions

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

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

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

NOTE: The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)
To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

13.2.2 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.
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).

13.2.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) Increases in size to ≥ 15 mm in the short axis, or

b) There is new pathological confirmation that it is disease (regardless of size).

c) New effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

13.2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (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*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ X wks. from study entry
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.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

***PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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.

13.2.5 Duration of Response

Duration of Overall Response

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

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.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks

14. DATA AND RECORDS (20-MAY-2019)

14.1 Data Management/Collection (20-JAN-2022)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff 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 in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

14.2 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule Completion Guidelines.

14.3 Summary of Data Submission

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. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting. Summary of Data Submission: Refer to the CTSU website.

See Section 8.3 for TRIAD account access and installation instructions. All imaging, anonymized via TRIAD, is securely stored in the IROC image archive at IROC Philadelphia QA Center.

Summary of All Data Submission: Refer to the CTSU website

14.4 Data Quality Portal (20-JAN-2022)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.
Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

14.5 Rave-CTEP-AERS integration (20-JAN-2022)

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that 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 that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

14.6 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design (17-FEB-2020)

This is a phase II biomarker-driven protocol designed to simultaneously evaluate the efficacy of multiple biomarker/ALK inhibitor combinations in previously treated ALK-positive non-squamous NSCLC patients. Depending on the mutation detected (including no mutation detected), patients will be either deterministically assigned to a particular agent or randomized to one of multiple agents, based on Table 15.1. For patients with a given mutation, they will be assigned to ALK inhibitors according the pre-specified priority (denoted as "A", "B", "C" in Table 15.1) as they are sequentially accrued into the study over time. Patients who have failed on a particular ALK inhibitor before will not be assigned to the same agent even if it is available for assignment per Table 15.1. When randomization is used for treatment assignments, e.g., patients with mutation G1202, I1171, L1196 or no ALK mutation, their respective randomization ratio will be initially set with equal weights, and gradually adjusted during the trial conduct to minimize any difference between the numbers of patients treated with different drugs, as patients' prior ALK inhibitor treatment history are unknown. The purpose of such adaptive randomization is to maximize the statistical power to address the primary objective, e.g., evaluating if a specific mutation is prognostic for a specific ALK inhibitor therapy (as compared to no ALK mutation).

We assume 660 patients will be screened with 600 evaluable mutation analyses, and approximately 50% of these patients would be expected to have a relevant mutation. For patients with a mutation, the maximum number of evaluable patients to be treated with any ALK inhibitor/mutation combination is 40. For patients with no ALK resistance mutations, the maximum number of evaluable patients to be treated with any ALK inhibitor is 60.

Table 15.1: Treatment assignments based on tumor mutations (600 evaluable patients total)
A= initially available for assignment (not applicable if previously treated with that agent)
B= available for assignment only after A slots filled for that mutation (not applicable if previously treated with that agent)
C= available for assignment only after A and B slots filled for that mutation (not applicable if previously treated with that agent)

Mutation	Projected Prevalence (%)*	lorlatinib	LDK378 (ceritinib)	alectinib	brigatinib	ensartinib	crizotinib	Pemetrexed ± Cisplatin or Carboplatin
G1202	23.6	A			A			

(including G1202del and G1202R)								
C1156Y	1.8	A		C	B			
I1171	7.3	A	A		A			
L1196 (including L1196M)	5.5	A	C	B	A	A		
V1180	1.8	A	C		B			
F1174	1.8	B		A	C			
Compound mutation	5.5	A						
ALK L1198F mutation (alone or in combination with another ALK mutation)	3.6						A	
MET amplification	7.3						A	
No ALK-resistance mutations**	41.8	A	A	A	A	A		A

*For illustration purpose only. The mutation prevalence are based on literature or personal communications, which may be inaccurate.
**Including no MET amplifications

Compound mutation = two or more resistance mutation excluding those with L1198F
L1189F/MET amplification = L1198F mutation alone or in combination, or no ALK mutation but any *MET* amplification

If additional relevant information becomes available, patients with a specified mutation may be able to be treated with more than of the 5 agents specified in Table 1. If other ALK mutations and relevant agents are discovered during the course of the trial, consideration by the trial investigators will be given to adding them to the trial by amendment.

15.2 Study Endpoints

15.2.1 Primary Endpoint

- Objective Response Rate (ORR), per investigator assessment

15.2.2 Secondary Endpoints

- Progression Free Survival (PFS), per investigator assessment
- Duration of Response (DOR), per investigator assessment
- Overall Survival (OS)
- Intracranial Objective Response Rate, per investigator assessment
- Safety profile

15.2.3 Correlative Science Endpoint

- Agreement of biopsy mutation result and cfDNA mutation result

15.3 Primary Objectives Study Design (17-FEB-2020)

15.3.1 Primary Hypothesis and Endpoints

For each subsequent ALK inhibitor therapy, the primary hypothesis is that the presence of a relevant resistance mutation (G1202/C1156Y /I1171/L1196/ V1180/ F1174/ compound mutation) is prognostic for objective response.

For the no ALK-resistance mutation patients, the primary hypothesis is to assess whether subsequent pemetrexed based chemotherapy improves objective responses as compared to ALK inhibitor therapies.

For the mutated cohorts (ALK L1189F or MET amplification) treated with crizotinib, the primary hypothesis is that crizotinib will result in a non-negligible response rate in respective patient cohorts.

The objective response rate (ORR) is defined as the number of subjects whose best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of evaluable subjects. BOR is defined as the best response designation, as determined by the investigators, recorded between the date of second step registration and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anticancer therapy, whichever occurs first. For subjects without documented progression or subsequent anticancer therapy, all available response designations will contribute to the BOR determination.

15.3.2 Primary Endpoint Analysis Plan

For each ALK inhibitor therapy, the primary analysis is to compare the response rate for those patients who have the relevant mutation (G1202/C1156Y /I1171/L1196/ V1180/F1174/compound mutation) to those patients who receive the same ALK inhibitor therapy who have no mutations using Fisher's exact test. All patients who receive at least one dose of an ALK inhibitor therapy will be included. We anticipate the ORR in the mutation group to be high (e.g., 50%), and the non-mutation group to be low (e.g., 10%). One-sided alpha level of 0.05 will be used.

For the no ALK-resistance mutation patients, the primary analysis is to compare patients who are randomized concurrently to the pemetrexed with cisplatin or carboplatin arm and the respective ALK inhibitor therapy arm, e.g., intent-to-treatment population. The response rates will be compared using Fisher's exact test. We anticipate the ORR in the non-targeted therapy to be moderately high (e.g., 35%), and the ALK inhibitor group to be low (e.g., 10%). One-sided alpha level of 0.05 will be used.

For cohorts with ALK mutation of L1189F or MET amplification, the primary analysis will be based on the optimal Two-Stage design testing the null hypothesis that ORR≤20% vs. the alternative ORR≥50% (See Section 15.4). All patients who receive at least one

dose of their assigned treatment regimen will be included.

The primary analysis of each mutation/agent combination cohort will be conducted when each cohort meets its accrual target and are potentially followed for at least 24 weeks follow-up for the purpose of evaluating BOR status. The ORR for each mutation/regimen combination and the associated 95% confidence intervals (using Clopper-Pearson method) will also be reported.

15.3.3 Sample Size and Power Calculations

Given the limited knowledge of the ALK mutation prevalence, this study cannot be designed to make an explicit hypothesis testing with uniform power and type 1 error consideration across all possible mutation/ALK inhibitor combinations. Instead, the study is designed to exploit the logistical efficiency of a protocol to simultaneously evaluate as many mutation/ALK inhibitor combinations as possible (with proper prioritizations).

For the primary objective of evaluating the prognostic value of mutations with respect to any specific ALK inhibitor, the statistical power for a particular comparison depends on the sample sizes actually accrued and the one-sided type 1 error specified. For example, for each ALK inhibitor, with one-sided 0.05 level testing, there would be 90% power to detect an improvement in response rates from 10% (n=40, no mutations) to 45% (n=25, a specific mutation), but only 81% power to detect an improvement in response rates from 10% (n=40, no mutations) to 50% (n=12, a specific mutation).

For the primary objective of evaluating the preferred regimen for no ALK-resistance mutation patients, with one-sided type 1 error of 0.05, there would be 78% power to detect an improvement in response rates from 10% to 35% (n=40 for each no mutation cohort).

These analyses need to be considered hypothesis generating because there are different mixes of patients in each group (in particular, different proportions of prior treatments).

For patients with a mutation, the maximum number of evaluable patients to be treated with any ALK inhibitor/mutation combination is 40. For patients with no ALK resistance mutations, the maximum number of evaluable patients to be treated with any ALK inhibitor or pemetrexed based chemotherapy is 60. These maximum number of evaluable patients to be treated are chosen to address the primary objectives and be consistent with two-stage designs for each mutation/drug combination cohorts as delineated in Section 15.4.

15.4 Study Monitoring of Primary Objectives (20-JAN-2022)

For each mutation (or no resistance mutation)/regimen, a two-stage design will be used to provide an opportunity to stop accrual early if we see too few responses such that we can minimize the number of patients treated with highly unlikely efficacious agents. The stopping criteria, however, are different for a mutation cohort and the no-ALK- mutation cohort.

For a no ALK-resistance mutation cohort treated with any ALK inhibitor or pemetrexed based chemotherapy, we consider an optimal two-stage design to evaluate non-negligible response rate by testing the null hypothesis that ORR≤5% vs. the alternative ORR≥20%. Such design has an expected sample size of 23.49 and a probability of early termination of 0.540. If a given ALK inhibitor or pemetrexed based chemotherapy is actually not effective, there is a 0.093 probability of concluding that it is (the target 1-sided alpha was 0.100). If the drug is actually effective, there is a 0.098 probability of concluding that it is not (the target power was 90%). After 12 eligible patients have been accrued and treated with at least one cycle of a given ALK inhibitor, accrual to that inhibitor will be suspended. Accrual will resume when at least one BOR of CR or PR is observed from the first 12 eligible patients; if one patient was already reported as having a BOR of CR or PR when the 12 patient accrual goal is reached, then accrual will not be suspended. Otherwise this no-mutation/drug combination cohort will be closed to accrual if none experience a BOR of either CR or PR after up to 24 weeks follow-up, in which case patients with no ALK-resistance mutations accrued in the future will be randomly assigned to the remaining available regimens. If patient accrual resumes after the stage 1 assessment, the stage 2 analysis of the two-stage design will be conducted for a given regimen or pemetrexed based chemotherapy when 37 eligible patients become analyzable (treated with at least 1 cycle of the inhibitor and potentially followed for at least 24 weeks). The drug will be considered inactive if less than or equal to 3 patients with a BOR of CR or PR are observed out of the 37 patients. For a no-mutation cohort treated with any ALK inhibitor or pemetrexed based chemotherapy, the accrual will remain open until the stage 2 analysis demonstrates the inhibitor is inactive, or a total of 60 patients have been accrued in this mutation/inhibitor cohort.

For a mutation cohort treated with any ALK inhibitor, we similarly consider an optimal two-stage design but with a higher bar of efficacy, i.e., to test the null hypothesis that ORR≤20% vs. the alternative ORR≥50% response rates. Such design has an expected sample size of 8.41 and a probability of early termination of 0.655. If the ALK inhibitor is actually not effective for this particular mutation, there is a 0.085 probability of concluding that it is (the target 1-sided alpha was 0.100). If the ALK inhibitor is actually effective, there is a 0.184 probability of concluding that it is not (the target power was 80%). After 6 eligible patients have been enrolled and treated with at least one cycle of the ALK inhibitor, the accrual to that inhibitor will be suspended. The accrual will resume when at least 2 BORs of CR or PR are observed from the first 6 eligible patients; if two patients were already reported as having a BOR of CR or PR when the 6 patient accrual goal is reached, then accrual will not be suspended. If no or one response is observed from the first 6 eligible patients after up to 24 weeks follow-up, this mutation/ALK inhibitor cohort will be closed to accrual, in which case patients with the same mutation accrued in the future will be randomly assigned to the remaining available ALK inhibitors (when applicable). If no ALK inhibitors are available for treatment assignment (including those with priority “B” or “C”), the accrual may remain open but the patients accrued after the patients required to complete the first stage analysis will not be included in the analysis of the first stage results. If patient accrual resumes after the stage 1 assessment, the stage 2 analysis of the two-stage design will be conducted when

13 eligible patients become analyzable (treated with at least 1 cycle of the ALK inhibitor and potentially followed for at least 24 weeks). The ALK inhibitor will be considered inactive for this mutation if less than or equal to 4 patients with a BOR of CR or PR are observed out of the 13 eligible patients. The accrual will remain open until the stage 2 analysis demonstrates the inhibitor is inactive, or a total of 40 patients have been accrued in this mutation/inhibitor cohort.

After the trial has accrued 100 patients, the accrual and frequency of mutations will be assessed. If it appears that an insufficient number of patients are being seen with a given mutation, a protocol amendment may be considered to adjust the slot assignments to ensure sufficient patients are seen in the highest priority agents at that time. For example, if it appears that insufficient I1171 patients are being seen, the three "A" slots for this mutation may be prioritized as A, B, and C slots instead.

The NRG Oncology Data Monitoring Committee (DMC) will be informed when the 2-stage design futility boundaries are met for each mutation/inhibitor cohort and no-mutation/drug cohort. In addition, DMC will review the study twice a year with respect to patient accrual and morbidity. An interim study summary report will be prepared at each meeting accordingly until all initial study results have been released. In general, the interim reports will contain information about patient accrual rate, a projected completion date for the accrual phase, patient exclusion rates and reasons following registration, compliance rate of treatment delivery, distributions of pretreatment characteristics and important prognostic baseline variables, and the frequencies and severity of treatment-related adverse events. The interim reports will not contain the results of any efficacy analyses.

The DMC also will review the study on an "as needed" basis.

15.5 Accrual/Study Duration Considerations

Guarding against up to a 10% rate of patients whose biopsies are unsuitable for mutation assessment, the total number of patients to be screened is up to 660. During the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional review boards (IRBs). Assuming a uniform monthly accrual rate of 8 patients and minimal accrual in the first 6 months for ramp-up, we project the accrual for the trial may last approximately 7.4 years. The rate of patients without evaluable biopsies will also be carefully monitored by the study team. If the rate is substantially different from the design assumptions, appropriate action plans, including protocol amendments may be made after discussions between NRG Oncology and NCI.

15.6 Secondary Endpoints and Statistical Analysis Plans

15.6.1 Statistical Analysis Plan for Efficacy Endpoints

The secondary efficacy endpoints include progression-free survival (PFS), duration of response (DOR), overall survival (OS), and intracranial objective response rate (ORR). They will be estimated for each mutation (or no mutation)/regimen combination.

PFS is defined as the time from second step registration to the date of the first recorded

occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1.

OS is defined as the time from second step registration to the date of death from any cause.

DOR is defined as the time from the first occurrence of a documented BOR of CR or PR to the first date of recorded disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. DOR will be derived for efficacy-evaluable patients (eligible patients with at least one cycle of ALK inhibitor) with a BOR of CR or PR.

The Kaplan-Meier method will be used to estimate the distribution and median for PFS, OS, and DOR, with 95% confidence intervals constructed through use of the Brookmeyer and Crowley method. PFS and OS rates at specific time-points will also be estimated using the Kaplan-Meier method, with 95% confidence intervals calculated on the basis of Greenwood's estimate for the variance.

Intracranial objective response rate (ORR) is defined as the rate of CNS response among patients with known CNS metastasis but no prior CNS radiation therapy. Patients who required additional treatment (for their non-cranial systemic disease) will be considered as non-responders (if they have not previously had an intra-cranial response). The associated 95% confidence intervals (using Clapper-Pearson method) will also be reported.

15.6.2 Statistical Analysis Plan for Safety Endpoints

For each patient, the maximum severity of reported adverse events assessed using NCI Common Terminology Criteria for Adverse Events (CTCAE, v. 5.0) will be used in all summaries. Adverse events will be summarized regardless of relationship to protocol treatment as assessed by the investigator. All adverse events, adverse events leading to withdrawal, interruption or modification of protocol treatment, Grade ≥ 3 adverse events, and serious adverse events will be summarized. Deaths and cause of death will be summarized. The rate of treatment-related adverse events will be reported with the frequency and severity (e.g., type, grade, and attribution). The safety analysis will be performed for cohorts if the respective stage 1 futility boundaries are not met.

15.6.3 Statistical Analysis Plan for Correlative Sciences

For each resistance mutation, the agreement of the biopsy result (present, absent, unavailable) and the cfDNA result (present, absent, unavailable) will be assessed at the end of the trial. There will also be an interim assessment of these results after 200 patients have been evaluated (accrual will not be suspended while awaiting these evaluations). These interim results will be discussed with the FDA to determine whether the agreement is high enough so that cfDNA mutation results could be substituted for the biopsy results in the remainder of the trial.

15.7 Gender/Ethnicity/Race Distribution

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	4	4	0	0	8
Asian	4	10	0	0	14
Native Hawaiian or Other Pacific Islander	4	4	0	0	8
Black or African American	35	39	0	0	74
White	238	269	18	31	556
More Than One Race	0	0	0	0	0
Total	285	326	18	31	660

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APPENDIX I: ANALYSIS PLANS FOR CFDNA RESULTS

Agreement of cfDNA and biopsy results will be considered separately for MET amplification and for the gene mutations. Note that an eligibility requirement is that the patient have an evaluable biopsy results for MET amplification and the gene mutations, but not necessarily a evaluable cfDNA results. Therefore, in the agreement tables that follow there is a category for unavailable cfDNA results but no such category for biopsy results. As it is possible to obtain a tumor biopsy after an unavailable cfDNA result, the agreement estimated will be restricted to patients who have both evaluable biopsy and evaluable cfDNA results. We will take the biopsy results as the reference standard. However, it is possible that cfDNA results may in some cases be more reflective of the tumor's biology than the biopsy results (because of tumor heterogeneity).

These analysis plans will be reviewed with the FDA prior to examining any agreement results from this trial.

Agreement for MET amplification results
At the end of the trial, the following table will be completed.

		cfDNA result			
		Present	**Absent**	**Unavailable**	**Total**
Biopsy result	**Present**	a	b		
	Absent	c	d		
	total				

The sensitivity and specificity of the cfDNA results for the biopsy results are given by a/(a+b) and d/(c+d), respectively. If the one-sided 95% lower confidence interval for the sensitivity is greater than or equal to 90%, and the one-sided 95% lower confidence interval for the specificity is greater than or equal to 90%, then the cfDNA MET amplification results will be deemed to agree sufficiently with the biopsy results to be used as a substitute. (The score method will be used to form the confidence limits.)

To get an idea of what observed agreement would be necessary to satisfy the above criterion, note the following: With approximately 600 patients with biopsy results, and assuming a 10% of the cfDNA results are unavailable and a biopsy MET amplification rate of 7.3% (Table 15.1), there would be 39 biopsy MET amplified patients and 501 biopsy non-MET amplified patients (with cfDNA results).

Therefore, an observed sensitivity of greater than 98.0% and an observed specificity of greater

than 92.3% would be needed to declare the cfDNA results a reliable substitute for the biopsy results.

Agreement for gene mutation results

At the end of the trial, the following summary table for the gene mutation results will be completed (gene mutation considered G1202, C1156Y, I1171, L1196, V1180, F1174, and L1198F):

		cfDNA result				
		Some mutations		No mutations	Unavailable	total
		Same as biopsy results	Some different than biopsy results			
Biopsy result	Some mutations	a	b	c		
	No mutations	N.A.	d	e		
	Total					

N.A. = not applicable

The sensitivity will be estimated by a/(a+b+c) and the specificity by e/(d+e).

In addition, an agreement table will be completed for each gene mutation separately: G1202, C1156Y, I1171, L1196, V1180, F1174, and L1198F. The table for G1202 is shown here:

G1202		**cfDNA result**			
		Present	**Absent**	**Unavailable**	**Total**
Biopsy result	**Present**	a	b		
	Absent	c	d		
	total				

For each gene mutation the sensitivity will be estimated by a/(a+b) and the specificity by d/(c+d).

The cfDNA gene mutation results will be deemed to agree sufficiently with the biopsy results to

be used as a substitute if both of the following two conditions are met:

(1) The one-sided *lower* 95% confidence limits for the overall sensitivity and specificity are greater than or equal to 90%.

AND

(2) For each mutation, the one-sided *upper* 99% confidence limits for the sensitivity and specificity are greater than or equal to 90%.

The rationale behind this decision rule is that as the methods for identifying the different gene mutations are the same, one would expect a priori the agreement to be the same or similar for the different genes. This justifies pooling the information and condition (1). However, we would not want to use the cfDNA as a substitute for the biopsy results if there was very strong evidence that the agreement was not adequate for one or more of the mutations. This justifies condition (2).

To get an idea of what observed agreement would be necessary to satisfy condition 1, we note the following: With approximately 600 patients with biopsy results, and assuming a 10% of the cfDNA results are unavailable and a rate of 50.9% for one or mutations being present (Table 15.1), an observed sensitivity of greater than 93.1% and an observed specificity of greater than 93.1% would be needed to declare the cfDNA results a reliable substitute for the biopsy results.

Interim Analysis of cfDNA results

The interim assessment for assessing agreement will occur when the first 200 patients have had their cfDNA results evaluated. We utilize the same decision rules given above to decide whether we could substitute cfDNA results for the remainder of the trial. Because of the relatively small numbers, the observed agreement will need to be very high to satisfy condition 1: For agreement concerning MET amplification, we would expect only about 13 patients to have biopsy MET amplification and evaluable cfDNA results. This translates into a required observed sensitivity of >99%, which means all the patients with biopsy MET amplification would also need to have cfDNA MET amplification. The observed specificity of the MET amplification would need to be greater than 93.9%.

For the gene mutations, one would expect about 90 patients to have some mutation and 90 patients to have no mutations, requiring an observed sensitivity and specificity of 95.3% to satisfy condition 1 above. To be able to substitute cfDNA results for biopsy results for the rest of the trial, the criteria would need to be satisfied for MET amplification and the gene mutations.

APPENDIX II: TECHICAL SPECIFICATIONS FOR FOUNDATIONONE®CDX SOLID TUMOR ASSAY (20-MAY-2019)

Technical Specifications

FOUNDATIONONE CDx™

Intended Use

FoundationOne CDx™ (F1CDx) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Table 1: Companion diagnostic indications

INDICATIONS	BIOMARKER	FDA-APPROVED THERAPY*
Non-Small Cell Lung Cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E or V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib), in combination with Zelboraf® (vemurafenib)
Breast Cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal Cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3 and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3 and 4)	Vectibix® (panitumumab)
Ovarian Cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

* Tarceva® is the registered trademark of OSI Pharmaceuticals, LLC. Zelboraf®, Herceptin®, Perjeta®, Kadcyla®, and Cotellic® are registered trademarks of Genentech, Inc. Gilotrif® is a registered trademark of Boehringer Ingelheim International GmbH. Iressa® and Tagrisso® are registered trademarks of the AstraZeneca group of companies. Xalkori® is a registered trademark of Pfizer Inc. Zykadia®, Tafinlar®, and Mekinist® are registered trademarks of Novartis AG Corporation Switzerland. Erbitux® is a registered trademark of ImClone LLC, a wholly owned subsidiary of Eli Lilly and Company. Alecensa® is a registered trademark of Chugai Seiyaku Kabushiki Kaisha. Vectibix® is a registered trademark of Immunex Corporation. Rubraca® is a registered trademark of Clovis Oncology, Inc.

Summary of Clinical Studies

Follow-on CDx claims were based on a non-inferiority statistical testing approach using the enrichment design presented in the paper by Li (2016).[1] All studies passed the acceptance criteria specific in each study protocol.

BIOMARKER	POSITIVE PERCENT AGREEMENT (PPA)†	NEGATIVE PERCENT AGREEMENT (NPA)	COMPARATOR METHOD*
EGFR Exon 19 Deletions and L858R	98.1% (106/108)	99.4% (153/154)	cobas® *EGFR* Mutation Test v2
EGFR T790M	98.9% (87/88)	86.1% (93/108)	cobas® *EGFR* Mutation Test v1 cobas® *EGFR* Mutation Test v2
ALK Rearrangements	92.9% (78/84)	100% (75/75)	Ventana *ALK* (D5F3) CDx Assay Vysis *ALK* Break-Apart FISH Probe Kit
KRAS	100% (173/173)	100% (154/154)	therascreen® *KRAS* RGQ PCR Kit
ERBB2 (HER2) Amplifications	89.4% (101/113)	98.4% (180/183)	Dako HER2 FISH PharmDx® Kit
BRAF V600	99.4% (166/167)	89.6% (121/135)‡	cobas® *BRAF* V600 Mutation Test
BRAF V600E	99.3% (149/150)	99.2% (121/122)	
BRAF V600 dinucleotide§	96.3% (26/27)	100% (24/24)	THxID® *BRAF* kit

* Cobas® is a trademark of Roche Diagnostics Operations, Inc. Therascreen® is a trademark of Qiagen. PharmDx® is a registered trademark of Dako Denmark A/S. THxID® is a registered trademark of bioMérieux.
† The reference standard used to calculate PPA and NPA is defined as the consensus calls between the two comparator methods – PPA being when FoundationOne CDx and the comparator method(s) identified mutations in mutated patients and NPA being when FoundationOne CDx and the comparator method(s) did not identify mutations in non-mutated patients.
‡ Sensitivity of dinucleotide detection of *BRAF* V600K and V600E was found to be significantly reduced in cobas® test, in particular for samples in which FoundationOne CDx detected the dinucleotides to be of lower than 40% mutant allele frequency (MAF), leading to low NPA values.
§ A study using the THxID® BRAF kit (bioMérieux) was conducted with samples with BRAF V600 dinucleotide mutation detected by F1CDx and BRAF V600 negative samples to provide a better evaluation of V600 dinucleotide concordance.

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Current Gene List[2]

Genes with full coding exonic regions included in FoundationOne CDx for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs).

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*	*EPHB4*
ERBB2	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*	*PARK2*
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*		*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QK1*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1 (MMSET)*	*WHSC1L1*	*WT1*
XPO1	*XRCC2*	*ZNF217*	*ZNF703*					

Select Rearrangements[2,3]

Genes with select intronic regions for the detection of gene rearrangements, one gene with a promoter region and one non-coding RNA gene.

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT (promoter only)***	
TMPRSS2								

**TERC* is non-coding RNA gene. ***TERT* is gene with promoter region

FoundationOne CDx™ is a next-generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. For the complete intended use statement, including companion diagnostic indications and warnings and limitations, please see the FoundationOne CDx Technical Information, *www.foundationmedicine.com/f1cdx*.

Reference

1. Li M. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study. Statistics in Biopharmaceutical Research 8, 355-363 (2016).
2. Current as of December 12, 2017. Please visit *www.foundationmedicine.com/f1cdx* for the most up-to-date gene list.
3. Refer to our full label for listing of intronic regions at *www.foundationmedicine.com/f1cdx*.

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APPENDIX III: SPECIMEN INSTRUCTIONS FOR FOUNDATIONONE®CDX SOLID TUMOR ASSAY (20-MAY-2019)

Specimen Instructions

FOUNDATIONONE CDx™

FoundationOne CDx™ is a broad companion diagnostic (CDx) test for five tumor indications. In addition to use as a companion diagnostic, F1CDx provides cancer relevant alterations that may inform patient management in accordance with professional guidelines. Information generated by this test is an aid in the identification of patients who are most likely to benefit from associated therapeutic products as noted in Table 1 of the Intended Use.[1]

Acceptable Samples

- Formalin-fixed paraffin embedded (FFPE) specimens, including cut slide specimens are acceptable.
- Use standard fixation methods to preserve nucleic acid integrity. 10% neutral-buffered formalin for 6–72 hours is industry standard. DO NOT use other fixatives (Bouins, B5, AZF, Holland's).
- Do not decalcify.

☐ **SAMPLE SIZE**

1 When feasible, please send the block + 1 H&E slide.*

10 unstained slides (positively charged and unbaked at 4-5 microns thick) + 1 H&E slide.*

*For smaller samples, providing the original H&E will preserve material for testing.

☐ **SURFACE AREA**

2 **MINIMUM: 25 mm²**

If sending slides, provide 10 unstained slides cut at 4-5 microns thick to achieve a tissue volume of 1 mm³.**

**Specimens with a smaller surface area may meet volume requirements by submitting additional unstained slides (USS) or block.

☐ **TUMOR CONTENT**

3 **OPTIMUM: 30% TN MINIMUM: 20% TN**

Percent tumor nuclei (%TN) = number of tumor cells divided by total number of all cells with nuclei

Note for liver specimens: higher tumor content may be required because hepatocyte nuclei have twice the DNA content of other somatic nuclei

Shipping Instructions

1. Place the samples, FoundationOne CDx™ requisition form, insurance information, and any other attachments into the FoundationOne CDx Specimen Shipping Kit.
2. Place the specimen shipping kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. blocks, slides) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack to:

Foundation Medicine, Inc.
150 Second Street
Cambridge, MA 02141
Phone: 888.988.3639

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Intended Use

FoundationOne CDx™ (F1CDx) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Table 1: Companion diagnostic indications

INDICATIONS	BIOMARKER	FDA-APPROVED THERAPY*
Non-Small Cell Lung Cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
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	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E or V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib), in combination with Zelboraf® (vemurafenib)
Breast Cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal Cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3 and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3 and 4)	Vectibix® (panitumumab)
Ovarian Cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

Reference

1. For full information on the intended use, assay descriptions, and for detailed performance specifications, refer to the complete FoundationOne CDx label at *www.foundationmedicine.com/f1cdx*.

* Tarceva® is the registered trademark of OSI Pharmaceuticals, LLC. Zelboraf®, Herceptin®, Perjeta®, Kadcyla®, and Cotellic® are registered trademarks of Genentech, Inc. Gilotrif® is a registered trademark of Boehringer Ingelheim International GmbH. Iressa® and Tagrisso® are registered trademarks of the AstraZeneca group of companies. Xalkori® is a registered trademark of Pfizer Inc. Zykadia®, Tafinlar®, and Mekinist® are registered trademarks of Novartis AG Corporation Switzerland. Erbitux® is a registered trademark of ImClone LLC, a wholly owned subsidiary of Eli Lilly and Company. Alecensa® is a registered trademark of Chugai Seiyaku Kabushiki Kaisha. Vectibix® is a registered trademark of Immunex Corporation. Rubraca® is a registered trademark of Clovis Oncology, Inc.

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APPENDIX IV: TECHNICAL SPECIFICATIONS FOR FOUNDATIONONE®LIQUID BLOOD-BASED ASSAY (20-MAY-2019)

Reporting

- Test results are provided in an interpretive report, curated by biomedical informatics scientists, and approved by board-certified and licensed pathologists.
- Genomic findings are listed with clinically relevant targeted therapies, immunotherapies, and clinical trials.
- Reported alterations may indicate response or lack of response to therapy (approved or in clinical trials), or may be drivers of oncogenesis based on reported scientific knowledge.
- Reports include microsatellite instability (MSI)* status, a biomarker that may help predict response to checkpoint inhibitors.
- Test results are available via our online portal at *www.foundationmedicine.com*† or by fax.

Additional Features

Mutant Allele Fraction (MAF)

The MAF listed denotes the frequency of the mutant allele identified in the sample. It is reported for base substitutions and insertions and deletions (indels).

Visualization of MAF

The clinical report includes a graphic representation of MAF. If multiple FoundationOne Liquid tests are ordered in the patient's treatment journey, the graphic will show the relative change in MAF which will allow treating physicians to better understand the evolution of a patient's disease and may help to inform the next steps in patient care.

Current Gene List‡

Entire coding sequence (base substitutions, indels, copy number alterations).

APC	*AR*	*ATM*	*BRCA1*	*BRCA2*	*CCND1*	*CD274 (PD-L1)*	*CDH1*	*CDK4*
CDK6	*CDK12*	*CDKN2A*	*CHEK2*	*CRKL*	*EGFR*	***ERBB2***	*ERRFI1*	*FGFR1*
FGFR2	*FOXL2*	***KRAS***	*MDM2*	*MET*	*MYC*	*MYCN*	*NF1*	*PALB2*
PDCD1LG2 (PD-L2)		***PTEN***	*PTPN11*	*RB1*	*SMO*	*STK11*	*TP53*	*VEGFA*

Select Exons§

ABL1	*AKT1*	*ALK*	*ARAF*	***BRAF***	***BTK***	*CTNNB1*	*DDR2*	*ESR1*
EZH2	*FGFR3*	***FLT3***	*GNA11*	*GNAQ*	*GNAS*	*HRAS*	*IDH1*	*IDH2*
JAK2	*JAK3*	***KIT***	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MPL*	*MTOR*	*MYD88*	*NPM1*
NRAS	*PDGFRA*	*PDGFRB*	*PIK3CA*	*RAF1*	***RET***	*ROS1*	***TERT***	

Select Rearrangements§

ALK	*EGFR*	*FGFR2*	*FGFR3*	*PDGFRA*	*RET*	*ROS1*

To learn more about our analytical validation based on a prior version of the test called FoundationACT (62 genes), see our publication in the Journal of Molecular Diagnostics:‖ "Analytical validation of a hybrid capture–based next-generation sequencing clinical assay for genomic profiling of cell-free circulating tumor DNA".

References

* Reported when MSI is determined to be high.
† Visit foundationmedicine.com to create an online account.
‡ Current as of August 2018. Please visit foundationmedicine.com for the most up-to-date gene list.
§ Detailed list available upon request.
‖ Clark TA, et al. Analytical validation of a hybrid capture–based next-generation sequencing clinical assay for genomic profiling of cell-free circulating tumor DNA. J of Mol Diagn. 2018;published online ahead of print.

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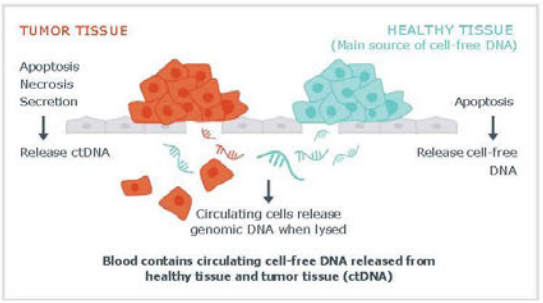
Technical Specifications

FOUNDATIONONE®LIQUID

FoundationOne®Liquid is a liquid biopsy test for solid tumors that analyzes circulating tumor DNA (ctDNA) in blood.

Clinical Background

Cell-free DNA (cfDNA) is DNA that circulates freely in the bloodstream. In a cancer patient, tumor cells that undergo apoptosis or necrosis also shed cell-free DNA. The tumor derived cell-free DNA is called circulating tumor DNA (ctDNA). By analyzing cell-free DNA isolated from a patient's blood, we can identify microsatellite instability (MSI)* and clinically relevant genomic alterations in ctDNA and may match them to targeted therapies, immunotherapies and clinical trials.



Blood contains circulating cell-free DNA released from healthy tissue and tumor tissue (ctDNA)

Methods

FoundationOne Liquid:

- Analyzes blood samples from patients with solid tumors including lung, breast, colon, etc.
- Uses a hybrid-capture, next-generation sequencing test method combined with proprietary computational algorithms that enable accurate variant calls by discriminating sequencing artifacts from bona fide mutations.
- Identifies four classes of genomic alterations (base substitutions, insertions and deletions, copy number alterations, and rearrangements), and reports high microsatellite instability.
- Evaluates select clinically relevant genomic alterations in 70 commonly altered oncogenes.
- Features an optimized laboratory process to achieve high sensitivity and specificity, with enhanced extraction methodology to generate a large amount of high quality ctDNA.
- Utilizes proprietary technology to accurately identify unique ctDNA fragments from plasma.

PERFORMANCE SPECIFICATIONS			
	Mutant Allele Frequency (MAF)/ **Tumor Fraction**[1]	**Sensitivity**[2]	**Positive Predictive Value** (PPV)[2]
Base substitutions	> 0.5%	99.9% (CI 99.7% – 99.9%)	100% (CI 99.9% – 100%)
	0.25% – 0.5%	95.8% (CI 94.5% – 96.9%)	99.8% (CI 99.3% – 99.9%)
	0.125% – 0.25%	68.4% (CI 65.7% – 70.9%)	96.1% (CI 94.8% – 97.1%)
Insertions/Deletions (Indels) (1–40bp)	> 0.5%	99.7% (CI 98.7% – 99.9%)	100% (CI 99.3% – 100%)
	0.25% – 0.5%	87.7% (CI 81.1% – 92.2%)	98.8% (CI 95.4% – 99.8%)
	0.125% – 0.25%	60.5% (CI 52.7% – 67.7%)	96.8% (CI 92.3% – 98.8%)
Rearrangements[3]	> 0.5%	100% (CI 85.9% – 100%)	100% (CI 85.9% – 100%)
	0.25% – 0.5%	89.4% (CI 65.5% – 98.2%)	100% (CI 77.1% – 100%)
	0.125% – 0.25%	68.4% (CI 43.5% – 86.4%)	100% (CI 71.7% – 100%)
Copy Number Amplifications (CNA)[4]	≥ 20%	95.3% (CI 82.9% – 99.2%)	97.6% (CI 85.9% – 99.9%)
	< 20%	Varies depending on amplitude of CNA and ctDNA fraction	
Microsatellite Instability (MSI)[5]	> 2.0%	92.0% (CI 72.5% – 98.6%)	100% (CI 82.2% – 100%)
Reproducibility (average concordance between replicates)		97.7% inter-batch precision 95.9% intra-batch precision	
Specimen Type		Peripheral whole blood (see Specimen Instructions for details)	
Turnaround Time[6]		< 2 Weeks	

1. Copy number amplifications were calculated using tumor fraction. 2. 95% confidence interval. 3. Performance for gene fusions within targeted introns only. Sensitivity for gene fusions occurring outside targeted introns or in highly repetitive intronic sequence contexts is reduced. 4. Copy number ≥ 8. 5. Reported when MSI is determined to be high. 6. Based on typical turnaround time from receipt of sample.

APPENDIX V: SPECIMEN INSTRUCTIONS FOR FOUNDATIONONE®LIQUID BLOOD-BASED ASSAY (20-MAY-2019)

Specimen Instructions

FOUNDATIONONE®LIQUID

Peripheral Whole Blood

Use only tubes provided inside the FoundationOne®Liquid Specimen Collection and Shipping Kit.
Other tubes will not be accepted.

Instructions For Use

Accurate analysis of cell-free DNA requires proper collection technique and handling of the sample. Failure to adhere to these instructions can compromise results by diluting cell-free DNA with DNA from white blood cell lysis.

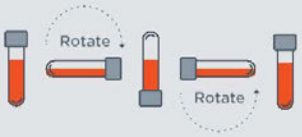
☐ 1 Check special tubes provided in FoundationOne Liquid kits to confirm liquid is clear and without cloudiness or crystals.

☐ 2 Label tubes with date of collection and two patient identifiers.

☐ 3 Collect two tubes of whole blood (8.5mL per tube).

- Prevent backflow: tubes contain chemical additives and it is important to avoid backflow into patient.
- Collect specimen by venipuncture according to CLSI H3-A6.[1]
- Fill tubes completely (8.5mL per tube).

☐ 4 Remove the tube from adapter and immediately **mix by gentle inversion 8 to 10 times.** Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180°, and back per the figure below.



☐ 5 Place specimen, completed requisition form (TRF) (remember to include patient's diagnosis), insurance information, available reports, and accompanying documents into the FoundationOne Liquid Specimen Collection and Shipping Kit (copies of pathology reports and/or other clinical documentation).

- Confirm each tube is labeled with the supplied labels indicating the date of collection and two unique patient identifiers (label included in kit).

☐ 6 Preferably on the same day of collection, ship via FedEx priority overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples.

Temperature is important. Keep at room temperature (43-99° F, 6-37° C).

DO NOT FREEZE.

Shipping Instructions

1. Place the samples, FoundationOne Liquid requisition form, insurance information, and any other attachments into the FoundationOne Liquid Specimen Collection and Shipping Kit.
2. Place the specimen kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. tubes) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack to:

Foundation Medicine, Inc.
150 Second Street
Cambridge, MA 02141
Phone: 888.988.3639

Reference
1. Clinical and Laboratory Standards Institute. H3-A6. Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard-sixth edition.

FOUNDATION MEDICINE

APPENDIX VI: CTEP COLLABORATIVE AGREEMENTS LANGUAGE

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

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.

APPENDIX VII: NRG-LU003 PILL DIARY FOR ALECTINIB

This pill diary is to be utilized for alectinib daily.

DP **NRG Oncology**
Phase II Biomarker-Driven Protocol for Previously Treated ALK-Positive NSCLC Patients
Pill Diary

NRG-LU003

NRG Patient ID

INSTRUCTIONS FOR THE PATIENT: Please record the date and number of tablets or capsules for each of the two time points specified daily (AM and PM). If a dose is missed or vomiting occurs after dosing, do not administer an additional dose, but do take the next dose at the scheduled time.

If you have any questions, contact:________________ Telephone:________________ Your next appointment is:__________

INSTRUCTIONS FOR INSTITUTION: This diary is provided as a daily list for the patient. This form is to be collected as source documentation and will be uploaded to Medidata Rave when each cycle is completed.

Month(s)_______________ **Year(s)**_______________________ **Treatment Cycle**___________

Drug name: Alectinib Drug dose: 600 mg Frequency: Twice per day

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________
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AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________

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APPENDIX VIII: NRG-LU003 PILL DIARY FOR BRIGATINIB

This pill diary is to be utilized for brigatnib only.

NRG Oncology
Phase II Biomarker-Driven Protocol for Previously Treated ALK-Positive NSCLC Patients
Pill Diary

NRG-LU003

NRG Patient ID

INSTRUCTIONS FOR THE PATIENT: Please record date and number of tablets or capsules taken daily. If a dose is missed or vomiting occurs after dosing, do not administer an additional dose, but do take the next dose at the scheduled time.

If you have any questions, contact:________________ Telephone:__________________ Your next appointment is:__________

INSTRUCTIONS FOR INSTITUTION: This diary is provided as a daily list for the patient. This form is to be collected as source documentation and will be uploaded to Medidata Rave when each cycle is completed.

Month(s)______________ **Year(s)**________________________ **Treatment Cycle**___________

Drug name: Brigatinib   Drug dose: 90 mg x 7 days, then 180 mg   Frequency: Once per day

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________

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APPENDIX IX: NRG-LU003 PILL DIARY FOR CRIZOTINIB

This pill diary is to be utilized for crizotinib only.

DP **NRG Oncology**
Phase II Biomarker-Driven Protocol for Previously Treated ALK-Positive NSCLC Patients
Pill Diary

NRG-LU003

NRG Patient ID

INSTRUCTIONS FOR THE PATIENT: Please record the date and number of tablets or capsules for each of the two time points specified daily (AM and PM). If a dose is missed or vomiting occurs after dosing, do not administer an additional dose, but do take the next dose at the scheduled time.

If you have any questions, contact_________________ Telephone:__________________ Your next appointment is:__________

INSTRUCTIONS FOR INSTITUTION: This diary is provided as a daily list for the patient. This form is to be collected as source documentation and will be uploaded to Medidata Rave when each cycle is completed.

Month(s)________________ **Year(s)**_________________________ **Treatment Cycle**____________

Drug name: Crizotinib Drug dose: 250 mg Frequency: Twice per day

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________
AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________	AM________ PM________

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APPENDIX X: NRG-LU003 PILL DIARY FOR ENSARTINIB (21-JUNE-2019)

This pill diary is to be utilized for ensartinib only.

DP **NRG Oncology**
Phase II Biomarker-Driven Protocol for Previously Treated ALK-Positive NSCLC Patients
Pill Diary

NRG-LU003

NRG Patient ID

INSTRUCTIONS FOR THE PATIENT: Please record date and number of tablets or capsules taken daily. If a dose is missed or vomiting occurs after dosing, do not administer an additional dose, but do take the next dose at the scheduled time.

If you have any questions, contact:________________ Telephone:_________________ Your next appointment is:__________

INSTRUCTIONS FOR INSTITUTION: This diary is provided as a daily list for the patient. This form is to be collected as source documentation and will be uploaded to Medidata Rave when each cycle is completed.

Month(s)_______________ **Year(s)**________________________ **Treatment Cycle**___________

Drug name: Ensartinib Drug dose: 225 mg Frequency: Once per day

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______

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APPENDIX XI: NRG-LU003 PILL DIARY FOR LDK378 (CERITINIB) (17-FEB-2020)

This pill diary is to be utilized for LDK378 (ceritinib) only.

DP **NRG Oncology**
Phase II Biomarker-Driven Protocol for Previously Treated ALK-Positive NSCLC Patients
Pill Diary

NRG-LU003

NRG Patient ID

INSTRUCTIONS FOR THE PATIENT: Please record date and number of tablets or capsules taken daily. If a dose of LDK378 (ceritinib) is missed, make up that dose unless the next dose is due within 12 hours. If vomiting occurs during the course of treatment, do not administer an additional dose and continue with the next scheduled dose of LDK378 (ceritinib).

If you have any questions, contact:________________ Telephone:__________________ Your next appointment is:__________

INSTRUCTIONS FOR INSTITUTION: This diary is provided as a daily list for the patient. This form is to be collected as source documentation and will be uploaded to Medidata Rave when each cycle is completed.

Month(s)_______________ **Year(s)**_______________________ **Treatment Cycle**___________

Drug name: LDK378 (Ceritinib) Drug dose: 450 mg Frequency: Once per day

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________
Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________	Number of tablets or capsules taken ________

APPENDIX XII: NRG-LU003 PILL DIARY FOR LORLATINIB

This pill diary is to be utilized for lorlatinib only.

DP **NRG Oncology**
Phase II Biomarker-Driven Protocol for Previously Treated ALK-Positive NSCLC Patients
Pill Diary

NRG-LU003

NRG Patient ID

INSTRUCTIONS FOR THE PATIENT: Please record date and number of tablets or capsules taken daily. If a dose is missed or vomiting occurs after dosing, do not administer an additional dose, but do take the next dose at the scheduled time.

If you have any questions, contact:________________ Telephone:_________________ Your next appointment is:__________

INSTRUCTIONS FOR INSTITUTION: This diary is provided as a daily list for the patient. This form is to be collected as source documentation and will be uploaded to Medidata Rave when each cycle is completed.

Month(s)_______________ **Year(s)**_______________________ **Treatment Cycle**___________

Drug name: Lorlatinib Drug dose 100 mg Frequency: Once per day

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______
☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______	☐ Number of tablets or capsules taken ______

NRG-LU003 DP 11-16-18 1 of 1

APPENDIX XIII: PROHIBITED THERAPIES, HERBAL SUPPLEMENTS AND MEDICATIONS TO BE USED WITH CAUTION

This is not an exhaustive list. Please consult a pharmacist for complete drug interactions. If a drug appears on more than one list, follow the most conservative rule. **It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as CYP inhibitors.**

CYP3A 4,5 Inhibitors (Strong)	CYP3A 4,5 Inhibitors (Moderate)	CYP34A 4, 5 Inhibitors (Weak)
Boceprevir	ACT-178882	Almorexant
Clarithromycin	Amprenavir	Alprazolam
Cobicistat (GS-9350)	Aprepitant	AMD070
Conivaptan	Atazanavir	Amiodarone
Danoprevir	Casopitant	Amlodipine
Elvitegravir	Ciprofloxacin	Atorvastatin
Fosamprenavir	Crizotinib	Azithromycin
Idelalisib	Darunavir	Berberine
Indinavir	Diltiazem	Bicalutamide
Itraconazole	Dronedarone	Blueberry Juice
Grapefruit Juice	Elvitegravir	Chlorzoxazone
Ketoconazole	Erythromycin	Cilostazol
LCL161	FK1706	Cimetidine
Lopinavir	Fluconazole	Clotrimazole
Mibefradil	Fosamprenavir	Cranberry Juice
Nefazodone	Imatinib	Cyclosporine
Nelfinavir	Ledipasvir	Daclatasvir
Posaconazole	Lomitapide	Delavirdine
Ritonavir	Schisandra sphehanthera	Everolimus
Saquinavir	Tipranavir/ritonavir	Faldaprevir
Telaprevir	Tofisopam	Fluvoxamine
Telithromycin	Verapamil	Fosaprepitant
Tipranavir		Gingko
Troleandomycin		Goldenseal
Voriconazole		GSK1292263
		GSK2248761
		Isoniazid
		Ivacaftor
		Lacidipine
		Liagliptin
		Lomitapide
		M100240
		Nilotinib
		Oral Contraceptives

		Pazopanib Peppermint Oil Propiverin Ranitidine Resveratrol Roxithromycin Seville Orange Juice Simeprevir Sitaxentan Suvorexant Tabimorelin Tacrolimus Teriflunomide Ticagrelor Tolvaptan Zileuton

CYP3A 4,5 Inducers (Strong and Moderate)	CYP3A 4,5 Inducers (Weak)
Avasimibe	Amprenavir
Bosentan	Aprepitant
Carbamazepine	Armodafinil
Efavirenz	AZD 7325
Enzalutamide	Bexarotene
Etravirine	Boceprevir
Genistein	Brivaracetam
Lersivirine	Clobazam
Lopinavir	Danshen
Mitotane	Dexamethasone
Modafinil	Echinacea
Nafcillin	Eslicarbazepine
Phenobarbital	Garlic
Phenytoin	Ginseng
Pioglitazone	Glycyrrhizin
Rifabutin	LCL161
Rifampin	Methylprednisolone
Ritonavir	Nevirapine
Semagacestat	Oritavancin
St. John's Wort	Oxcarbazepine
Thioridazine	PA-824
Tipranavir	Pleconaril
	Prednisone

CYP2C8 Inhibitors (Strong)	CYP2C8 Inhibitors (Moderate)	CYP2C8 Inhibitors (Weak)	CYP2C8 Inducers (Strong)
Gemfibrozil	Trimethoprim	Fluvoxamine Glitazones Ketoconazole Montelukast Quercetin	Rifampin

CYP2C9 Inhibitors (Strong)	CYP2C9 Inhibitors (Moderate)	CYP2C9 Inhibitors (Weak)
fluconazole	Amiodarone Felbamate Fluconazole Miconazole Piperine	Diosmin Disulfiram Fluvastatin Fluvoxamine Voriconazole

APPENDIX XIV: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD FOR ENSARTINIB (21-JUNE-2019)

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 drug, **ensartinib (X-396 HCl)**. 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:

Ensartinib may interact with certain specific enzymes in your liver.

- The enzymes in question are **CYP3A4 and 2C9**. Ensartinib is broken down mainly by CYP 3A4 and may be affected by other drugs that inhibit or induce this enzyme. Ensartinib inhibits CYP 3A4 and 2C9 and may affect other drugs that are broken down by these enzymes.
- Ensartinib is highly protein bound. Patients receiving other medications that are also highly protein bound may need to be monitored more frequently.

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

Ensartinib 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:

Ensartinib must be used very carefully with other medicines that use certain liver enzymes to be effective. 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 inhibitors or inducers of CYP3A4 and substrates of CYP3A4 and 2C9.

- 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.

- You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound
- 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

_____.

January 2017

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **ensartinib (X-396 HCl).** This clinical trial is sponsored by the NCI. **Ensartinib** 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. ➢ You may need to be monitored more frequently if you are receiving other medications that are also highly protein bound.	**Ensartinib interacts with specific liver enzymes called CYP3A4 and 2C9** and must be used very carefully with other medicines that interact with these enzymes. ➢ 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 inhibitors or inducers of CYP 3A4 and substrates of CYP3A4 and 2C9.** ➢ 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

APPENDIX XV: PATIENT CLINICAL TRIAL WALLET CARD (20-JAN-2022)

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov