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Harold C. Simmons Cancer Center

Phase II trial of Ceritinib in combination with Stereotactic Ablative Radiation (SABR) in *ALK*-rearranged metastatic lung adenocarcinoma

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Signature Page

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

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List of abbreviations

AE	Adverse Event
ALCL	Anaplastic large cell lymphomas
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BCRP	multidrug transporter ABCG2
b.i.d.	bis in diem/twice a day
CNS	Central nervous system
CR	Complete Response
CrCl	creatinine clearance
CRO	Contract Research Organization
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EIAED	enzyme inducing anti-epileptic medication
EGFR	epidermal growth factor receptor
EOT	End of treatment
FAS	Full Analysis Set
GI	Gastric intestinal
hERG	human Ether-à-go-go-Related Gene
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous (ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
LLN	Lower limit of normal
LLNA	local lymph node assay
MTD	Maximum Tolerated Dose
NSCLC	non-small cell lung cancer
o.d.	omnia die/once a day
OS	Overall survival
OTC	over-the counter
QD	once daily
PD	Progressive disease
p.o.	per os/by mouth/orally
PFS	Progression free survival
PHI	Protected Health Information
PK	Pharmacokinetics
PPI	proton pump inhibitors
PR	Partial response

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Racc	accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response Rate
SABR	Stereotactic Ablative Radiation
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TDI	time-dependent inhibition
TKI	tyrosine kinase inhibitors
ULN	upper limit of normal
UV	Ultraviolet radiation
VATS	Video-assisted thoracic surgery
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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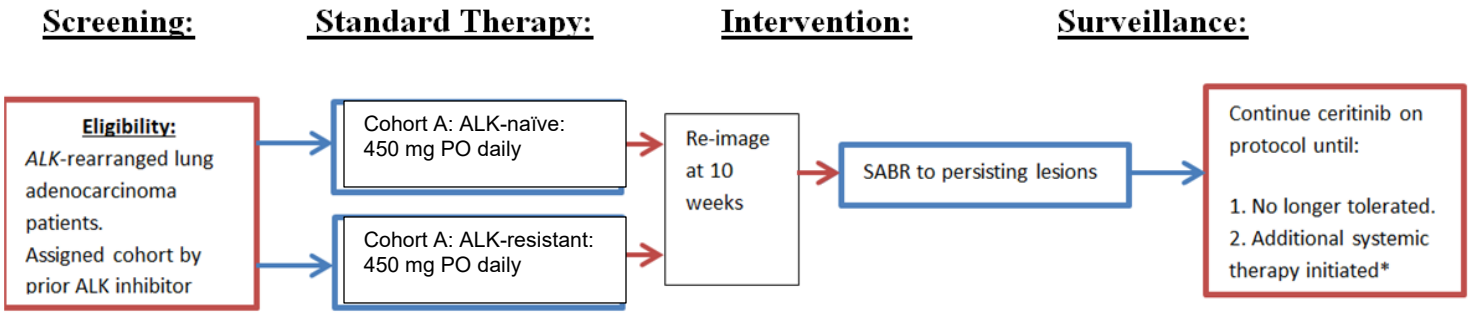
Protocol summary



*Additional SABR to progressive lesions **will be** allowed while on study after the initial radiation therapy at 10-weeks if clinically indicated.

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STUDY SUMMARY

Title	Phase II trial of Ceritinib in combination with Stereotactic Ablative Radiation in *ALK*-rearranged metastatic lung adenocarcinoma
Short Title	Ceritinib and SABR in *ALK* + lung adenocarcinoma
Protocol Number	XXX
Phase	II
Methodology	Open label, Dual arm
Study Duration	Three years
Study Center(s)	single center
Objectives	Prolongation of progression free survival in lung adenocarcinoma with targeted therapy and radiation
Number of Subjects	33
Diagnosis and Main Inclusion Criteria	Metastatic/locally advanced lung adenocarcinoma harboring a *ALK* rearrangement
Study Product(s), Dose, Route, Regimen	Ceritinib (LDK378) 450 mg PO daily
Duration of administration	Until progression/intolerance of therapy. Projected 14 months for patients who progressed on crizotinib therapy and 20 months for those who have not been treated previously with an ALK inhibitor.
Reference therapy	Published progression free survival with ceritinib (LDK378) alone
Statistical Methodology	Sample size calculated on the basis of prolongation of progression free survival of patients treated on this protocol compared to published survival data. Kaplan Meier Methods will be used to estimate progression-free survival and overall survival

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1.0 Background and Rationale

1.1 Overview of lung adenocarcinoma pathology, epidemiology and current treatment

1.1.1 Lung adenocarcinoma and molecular/genetic abnormalities

Lung cancer is the most common cancer worldwide. There are over 1.5 million cases annually, leading to more than 1 million deaths every year [1]. In the US, 160,000 deaths occur from lung cancer annually [2].

Lung cancer is classified broadly into small cell and non-small cell. Non-small cell lung cancer is further classified into squamous cell cancer and adenocarcinoma. Treatment for each classification varies, as well as their clinical behavior and molecular/genetic profile.

Lung adenocarcinoma has been found to harbor mutations that can be targeted with specific anti-cancer agents. These have dramatically improved the outlook for the minority of patients that do harbor an actionable mutation. These drugs are much better tolerated than traditional chemotherapies, with fewer side effects and also easier to take. However the duration of response to these targeted therapies is limited by the development of clinical resistance.

1.1.2 Treatment for *ALK*+ lung adenocarcinoma

Patients with lung adenocarcinoma now routinely have molecular/genetic testing performed on their tumor. Approximately 2-8% of patients with lung adenocarcinoma demonstrate a rearrangement in the anaplastic lymphoma kinase (*ALK*) gene [3, 4]. Due to the large number of lung cancer cases annually, this small percentage represents thousands of patients every year in the US.

ALK was identified as a chromosome translocation-produced protein in anaplastic large cell lymphomas (ALCL). In lung cancer, a fusion was identified between *ALK* and the echinoderm microtubule-associated protein like 4 (EML4-*ALK*) [3].

Patients with *ALK* rearrangements tend to be younger with less smoking history. The exact cause of the rearrangement is unclear. *ALK* rearrangements are rarely found in squamous cell cancer.

Crizotinib has been tested as an oral *ALK*-inhibitor. This compound has dramatically transformed treatment for *ALK* positive lung cancer. Crizotinib resulted in clinical response rates in more than 50% of 255 patients treated [5]. The median duration of response was 9-11 months. Crizotinib is FDA approved for the treatment of *ALK* positive lung cancer.

The NCCN guidelines recommend *ALK* inhibitor therapy be the first treatment for patients with *ALK* positive lung cancer [6]. However, the response to crizotinib is not durable, with many patients demonstrating progression within one year of treatment initiation. The central nervous system is a common site of progression [7].

Ceritinib is a second generation *ALK* inhibitor with 20 times greater potency. 246 patients were treated with ceritinib in a phase I trial [8]. 163 had previously been treated with an *ALK* inhibitor and 83 were *ALK*-inhibitor naïve. The overall response rate was 58%, with median duration of response being 10 months for those not previously treated with an *ALK* inhibitor, and 6.9 months for those previously treated

1.1.3 Combination of targeted therapy with stereotactic radiation

Stereotactic ablative body radiation (SABR) is a technique of delivering precisely targeted radiation to tumors while minimizing the dose given to adjacent normal tissue. Large doses of radiation are delivered in a small of number of treatments. Due to the radio-biological response to this type of radiation, there can be dramatic tumor responses leading to the ablative terminology.

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SABR has an increasing role in metastatic non-small lung cancer, as demonstrated by a recently concluded Phase II trial of targeted therapy with SABR [11]. This trial was conducted at UT Southwestern and enrolled 24 patients with advanced, metastatic non-small cell lung who had progressed on standard chemotherapy. These patients were with the targeted therapy erlotinib combined with stereotactic ablative radiation to sites of visible disease. In a previous trial, patients with advanced non-small cell lung cancer who had progressed after one cycle of chemotherapy and were then treated with erlotinib had a progression free survival (PFS) of 2.3 months and overall survival (OS) of 6.7 months [12]. Combining SABR with erlotinib trial prolonged the median PFS to 14.7 months and median OS to 20.7 months.

This combination of SABR with targeted therapy greatly prolonged the duration of time that targeted therapy was beneficial for patients. The study population was enriched for patients with limited metastatic disease, though it is plausible that patients with more advanced disease would also receive some benefit of the combined therapy.

1.1.4 Patterns of failure in non-small cell lung cancer

Reasons for discontinuing anti-cancer therapy include ineffective control of existing lesions or the development of new lesions. The patterns of failure in non-small lung cancer were evaluated in 64 patients with advanced non-small lung cancer [13]. 64% of patients in this study demonstrated progression in already known sites of disease. This suggests that enhanced control of existing lesions will result in prolongation of the benefit from systemic therapy.

1.1.5 Concept

The proposed study is designed to prolong the clinical benefit of *ALK*-inhibitor targeted therapy in patients with *ALK*+ lung cancer. This will evaluate the combination of two well-tolerated therapies, ceritinib and SABR. This dual therapy is expected to be more effective than either alone in destroying sensitive tumor cells and also in preventing the development of resistant cells.

Based on current studies, patients derive benefit from *ALK* inhibitors for less than a year before they need to be switched to another treatment, usually chemotherapy.

Ceritinib alone is active therapy, however resistance and progression will develop as with all ALK inhibitors. Tumors that remain after 10 weeks of ceritinib monotherapy may harbor weakly sensitive or resistant clones. While on systemic therapy, progression usually occurs at sites of known disease. Therefore targeting known and visible disease may delay progression that requires a change in systemic therapy.

This study will treat lesions that persist after 10 weeks of targeted therapy with ceritinib with stereotactic ablative radiation. Limited progression after that period will also be considered for repeat SABR if possible, instead of discontinuing the ceritinib that is keeping the majority of the disease under control. This accurately reflects current clinical practice and recommendations from the national authorities such as the NCCN, which recommend continuing targeted therapy after progression in some cases.

1.2 Immunologic effect of SABR and targeted therapy

The exact mechanism is not well defined, but the combination of an effective drug with ablative radiotherapy demonstrates a synergistic immune response.

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Ablative radiotherapy to a primary tumor leads to recruitment of CD8+ cells of the immune system in destroying cancer cells. Other mechanisms include disruption of immunologic barriers, enhanced antigen presentation to dendritic cells and potentially reversing tumor cell unresponsiveness in patients [14]. The decrease in size of untreated metastatic lesions after primary site ablative radiotherapy is termed the “abscopal effect” and has been demonstrated in solid tumors such as melanoma [15, 16].

The immunologic impact of administering radiation with ceritinib will be evaluated in tumor specimens. These would include modulators of immune response such as myeloid derived suppressor cells, macrophages, CD4/CD8 T-cells and NK cells. Analysis of blood specimens for myeloid derived suppressor cells and macrophages that are VEGF-R2 positive will also done to determine if serum changes correlate with response.

Research at UT Southwestern has demonstrated that ALK signaling leads to a pro-metastatic phenotype in breast cancer [17]. Macrophages are constituents of blood that can be divided into two broad subtypes M1 and M2. M1-like macrophages produce inflammatory cytokines and are capable of destroying tumor cells. M2-like macrophages promote collagen deposition and angiogenesis. They also secrete angiogenic and anti-inflammatory cytokines such as IL-10, TGF-β and VEGF which promote tumor progression.

Induction of the ALK pathway by pleiotropin is associated with macrophages that promote anti-inflammation, angiogenesis, immune tolerance and metastasis. These data suggested that ALK inhibition may be an effective in reducing metastatic spread from primary lung cancer. This also suggests that blood monitoring of M1 and M2 like macrophages may predict for the subsequent development of metastases.

1.3 Introduction to investigational treatment(s) and other study treatment(s)

1.3.1 Overview of Ceritinib

Ceritinib [5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2 (isopropylsulfonyl) phenyl]-2,4-pyrimidinediamine] is an orally available *ALK* inhibitor. Ceritinib in pre-clinical studies is an approximately 20-fold more potent *ALK* inhibitor than crizotinib, it is more selective for *ALK* and does not inhibit MET. In addition, ceritinib shows potent antitumor activity in crizotinib-resistant animal models (as described below) and the efficacy seen in the Phase I clinical trial in patients who failed crizotinib has been extremely encouraging (Mehra et al 2012; unpublished data summarized below). These features support the use of ceritinib in NSCLC patients whose disease has progressed on crizotinib.

1.3.1.1 Non-clinical experience

1.3.1.1.1 Pharmacology

Ceritinib inhibits *ALK* and *ALK*-mediated signaling pathways in a dose-dependent manner. It inhibits autophosphorylation of *ALK*, *ALK*-mediated phosphorylation of downstream signaling proteins, and proliferation of *ALK*-dependent cancer cells both *in vitro* and *in vivo*. Ceritinib is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of the *ALK* kinase activity (IC50 of 0.15 nM for ceritinib and 3 nM for crizotinib). In a kinase panel of 35 additional enzymes, demonstrated a high degree of selectivity for *ALK* inhibition by inhibiting only 2 other kinases (INSR and IGF1R) but with approximately 50-fold less potency than *ALK* inhibition.

Preclinical data showed inhibition of the kinase activity of the NPM-*ALK* fusion oncogene (in Karpas299 human ALCL cells) and of the EML4-*ALK* fusion oncogene (in H2228 human NSCLC cells) with ceritinib, which led to inhibition of cancer cell proliferation in vitro. The inhibition of the downstream signaling pathway by ceritinib correlated with the inhibition of proliferation. In addition, inhibition of NPM-*ALK* and EML4-*ALK* in mouse and rat xenograft models resulted in inhibition of tumor growth and tumor

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regression *in vivo*. Ceritinib was also active in cell lines with *ALK* amplification or expression of activating point mutations. A single dose pharmacodynamic study and multiple daily dose efficacy study performed in Karpas299 and H2228 tumor models indicated that a 70% to 80% reduction in the *ALK* signaling pathway is required to achieve complete tumor regression.

1.3.1.1.2 Nonclinical pharmacokinetics (PKs) and metabolism

Ceritinib showed good oral bioavailability (48%-100%) in various animal species. Ceritinib is highly bound to plasma protein (>94%) in all species. Following oral administration of [^{14}C]ceritinib to LEH male rats, radioactivity was widely distributed. The highest tissue exposures were found in intestine wall, uveal tract, pituitary gland, bile, adrenal cortex, harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla and pancreas (25 to 710-fold higher exposure relative to blood) [DMPK R0900773B]. Unchanged ceritinib was the major component in feces and bile of intact and bile duct-cannulated rats. In the rat, ceritinib underwent oxidation leading to the formation of five oxygenated metabolites (designated as M23.6, M30.6, M35.8, and M33.4). In addition, ceritinib underwent sulfation leading to M36.8 and oxidation followed by sulfation resulting in the presence of M29.5. Ceritinib also underwent glucuronidation leading to M26.8 and M27.6. The major metabolite in feces was designated M33.4 (oxygenation) accounting for approximately 7% of the dose. All other metabolites in feces and bile were minor (<5% of the dose). In rats dosed with [^{14}C]-ceritinib, ceritinib-derived radioactivity was excreted predominantly via the fecal route (>99%), and renal excretion was a minor pathway for excretion (<1%) [DMPK R0900773A]. Fecal excretion was the result of biliary excretion (69%) and gastrointestinal (GI) secretion (31%). Since parent drug was the major component in bile and feces after IV administration, enterohepatic circulation may occur.

CYP3A4/5 is the major hepatic enzyme metabolizing ceritinib in a human *in vitro* system. The compound is a time-dependent CYP3A4/5 inhibitor (K_I: 1.47 µM and k_{inact} 0.0642 min^{-1}), and a potent reversible inhibitor of CYP2A6 (Ki: 0.0316 µM), 2B6 (IC_{50} 2 µM), 2C8 (IC_{50} 2 µM), 2C9 (Ki: 0.241 µM) and 3A4/5 (Ki: 0.161 µM). These data suggest a high potential of drug-drug interaction between ceritinib and compounds metabolized by these CYP isoforms if sufficiently high concentrations of ceritinib are achieved. Ceritinib is likely a P-gp, but not BCRP or MRP2 substrate. It does not inhibit P-gp, BCRP or MRP2 up to 1.5 µM *in vitro*.

Kinetic PK/pharmacodynamic modeling was performed in the nude rat H2228 model (constitutively expressing ELM4-*ALK* gene) and the nude rat Karpas 299 model (expressing NPM-*ALK*). The minimal pharmacologic dose in humans was estimated to be 100 mg/day for tumor stasis.

1.3.1.1.3 Safety pharmacology and toxicology

Ceritinib was evaluated for safety in 2- and 4-week studies in rats and monkeys. The principal toxicity induced by ceritinib was a systemic inflammation characterized by increased neutrophil counts in the peripheral blood and mixed cell/neutrophilic inflammation of the biliopancreatic ducts, pancreas, and/or duodenum. Gastrointestinal toxicity was observed in both species characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and ampullae of rats and monkeys, respectively. Liver (bile duct) was also affected in both species only at the highest dose levels studied (100 mg/kg/day in the 2-week studies for both rat and monkeys and 50 and 30 mg/kg/day in the 4-weeks studies in rat and monkeys, respectively), and included increases in liver transaminases in a few animals at high doses, and mixed cell inflammation, erosion and cytoplasmic vacuolation of the bile duct epithelium. The pancreas was a target organ in the rat, but not the monkey, with acinar cell atrophy and mixed cell inflammation noted at mid- and high doses. Target organ effects showed partial to complete recovery during the 4-week non-dosing period. No effects in the rat central nervous system or on the respiratory system were observed at single, high doses (100 mg/kg).

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Ceritinib has potent activity on the hERG channel with an IC_{50} of 0.4 μM. However, there were no ceritinib-related effects in vivo in monkeys at doses as high as 100 mg/kg (human equivalent dose [HED] of 1950 mg).

Preclinical studies (*in vitro* 3T3 NRU assay, refer to [Investigators Brochure]) indicate a low risk of photo toxicity with use of ceritinib. In addition, a preliminary analysis from an *in vivo* UV LLNA assay demonstrates no significant phototoxic potential with ceritinib.

1.3.1.2 Clinical experience

1.3.1.2.1 Clinical safety, efficacy and tolerability

The phase I study of ceritinib demonstrated preliminary evidence of antitumor activity in *ALK*-positive NSCLC. The majority of these patients in this trial had received prior chemotherapy (median of 3 regimens) and the majority also received prior crizotinib. Among 114 response-evaluable patients with at least 18 weeks of follow-up, or who discontinued study earlier, and were treated with ceritinib doses of 400 mg daily or higher, 66 (58%) patients have responded. The response rate to ceritinib is similar regardless of prior *ALK* inhibitor therapy. In patients with NSCLC treated at ≥400 mg daily, who had previously received crizotinib, the response rate was 57%, and in those who had not previously received crizotinib it was 60%. Post-baseline tumor measurements are available for 104 of the 114 response evaluable patients. A waterfall plot displaying the maximum decrease from baseline in the sum of the longest tumor diameters (Figure 1-1) shows that the large majority of patients treated with ceritinib had a reduction in tumor burden. The median duration of response in patients who responded and were treated at ≥400 mg daily was 8.2 months (95% CI: 6.9, not estimable), and 71% had a duration of response of 6 months or longer.

After treatment with ceritinib, responses were seen in the CNS in lesions that were not treated with any other modality. The available data from the phase I study indicate that ceritinib has substantial antitumor activity in chemotherapy-treated *ALK*-positive NSCLC patients regardless of prior *ALK* inhibitor therapy.

In the Phase I trial of ceritinib [8], dose-limiting toxicities included diarrhea, vomiting, nausea, dehydration, hypophosphatemia and elevated alanine transferase. The most common adverse events included nausea (82%), diarrhea (75%), vomiting (65%), fatigue (47%), and increased alanine aminotransferase levels (21%). The common grade 3 or 4 adverse events were increased alanine aminotransferase (21%), increased aspartate aminotransferase (11%), diarrhea (7%), and increased lipase levels (7%).

1.3.2 Rationale of continuing systemic therapy after oligoprogression

This continuation of erlotinib beyond progression is recommended by the NCCN guidelines for the following benefits; delayed symptoms, reduction in tumor size and FDG avidity on PET [6, 18]. Similarly the continuation of *ALK*-inhibitors after the development of progressive disease has also been associated with clinical benefit. However the optimal therapy to combine with targeted therapy beyond progression is ill-defined as adding systemic chemotherapy is often too toxic.

In select patients continuing crizotinib beyond progression resulted in an overall survival of 29.6 months compared to 10.8 months for patients who did not continue crizotinib [19]. These data suggest that for a carefully selected group of patients, continuing *ALK* inhibitors even in the setting of limited progressive disease results in clinically meaningful benefit.

The decision to continue ceritinib at the time of oligoprogression will be at the discretion of treating oncologist in line with standard clinical practice. If, in the opinion of the treating oncologist, the patient would benefit from continued ceritinib this will be allowed even after documented oligoprogression.

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1.3.3 Rationale of adding stereotactic ablative radiation therapy after targeted therapy

SABR will be added as a cytoreductive agent after major cancer cell killing is achieved with ceritinib. This proposed study will evaluate the combination of two well-tolerated therapies, ceritinib and Stereotactic Ablative Radiotherapy (SABR). This dual therapy is expected to be more effective than either alone in destroying sensitive tumor cells and also in preventing the development of resistant cells.

Ceritinib alone is active therapy, however resistance and progression will develop as with all ALK inhibitors. Tumors that remain after 10 weeks of ceritinib monotherapy are likely to harbor weakly sensitive or resistant clones. The Goldie-Coldman hypothesis of tumor resistance [20] suggests that any detectable tumor will contain some resistant clones. According to this hypothesis, the probability of resistance developing in a tumor depends on i. the number of cancer cells and ii. the mutation rate of the constituent cells [21].

Stereotactic radiation to lesions that persist despite ceritinib therapy will effectively provide a non-invasive tumor “debulking” and reduction in tumor cell number. Fewer cancer cells may then result in a smaller chance of resistant clones developing according to the Goldie-Coldman hypothesis. Because of the reduced cancer cell number, this approach may prolong the time that ceritinib will be effective as the sole systemic therapy for *ALK*-rearranged patients. This will likely delay the development of clinically significant resistance that necessitates a switch from ceritinib to another systemic therapy.

Larger tumors are more heterogeneous and therefore more likely to contain some resistant cells, decreasing the chance of cure. To prevent resistance, according to Goldie-Coldman, it is suggested that multiple therapies should be used in combination whenever possible [21]. This allows for the therapies to achieve maximum efficacy against heterogeneous cell populations.

At study entry:
Patients on this trial who have lesions requiring radiation prior to initiation of systemic therapy in the view of the treating physician will be allowed to get such radiation. This will not limit their trial participation, though the lesion will be noted as having been radiated.

After 10 weeks of ceritinib monotherapy:
Lesions that persist after ceritinib monotherapy will receive stereotactic radiation. These include lesions that may have progressed during ceritinib monotherapy alone. As long as no change in systemic therapy is indicated, these patients will continue on the trial. Up to 6 sites or organs will receive stereotactic radiation, at the discretion of the treating physician. All sites of gross tumor (typically defined by CT and PET) should be treated for patients to continue on study.

Subsequent areas of progression:
As long as the study participant is on ceritinib as the sole systemic therapy, further stereotactic radiation may be delivered to up to 6 sites or organs at a time. When ceritinib is no longer the systemic agent or when new progressive sites cannot feasibly be treated with stereotactic radiation (e.g., malignant pleural effusion or site previously irradiated), study participation will end. The primary endpoint of progression-free survival will be calculated from the start of treatment to the first episode of progression.

Ceritinib during stereotactic radiation:
Currently there are limited data about the safety of concurrent ceritinib and stereotactic radiation, though studies are ongoing. If there is a concern for the safety of the patient, ceritinib will be held for 3

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days prior to and 3 days after the stereotactic radiation. The total expected duration of the stereotactic radiation is expected to range between 1-5 treatments, generally not exceeding 21 days from first to last radiation therapy.

CNS metastases:
Stereotactic radiation to CNS lesions that require therapy will be allowed. At study entry the presence of CNS lesions or their treatment with radiation will not constitute a restriction to study participation. Subsequently, progression in the CNS will not terminate study participation, and patients may receive stereotactic radiation to those areas.

Evaluation of CNS metastases will consist of an MRI or contrast enhanced CT performed at baseline and then as clinically indicated, but at least every 3 months . Patients without CNS involvement will not be required to have mandatory CNS imaging. All patients with new symptoms suspicious of CNS involvement will have urgent CNS imaging performed.

1.4 Study rationale and purpose

Patients with *ALK*+ non small cell lung cancer will receive the current optimal therapy with ceritinib. After 10 weeks of targeted therapy, there will likely be some persisting lesions that would not have completely regressed. These persisting lesions would likely consist of cells that are less sensitive to targeted therapy. From the data summarized above [13], these persisting lesions are most to subsequently develop resistance and demonstrate progression.

To delay the onset of clinical progression, lesions that persist after 10 weeks of ceritinib therapy and are amenable to stereotactic ablative radiation will be radiated. Ceritinib will be held for 3 days before the first dose of radiation and resumed 3 days after the last dose. There is no specific window for radiation. SABR should be initiated as feasible following at least 10 weeks of ceritinib treatment.

After radiation, all patients will continue ceritinib therapy. If subsequently there is any evidence of progression, there will be an assessment of whether a repeat course of radiation is feasible. If it is feasible to repeat SABR to sites of progression, this will be performed and ceritinib resumed. If SABR is not possible, then a change in systemic therapy will be required.

1.5 Rationale for the protocol design

The purpose of the trial is to determine if the addition of SABR to ceritinib can prolong the clinical benefit of targeted therapy. This will be an open-label, non-randomized, two arm trial in *ALK* + lung adenocarcinoma. The protocol will also report the safety of treating with SABR and ceritinib, though both are widely used in clinical practice.

Crizotinib is widely used for *ALK* + lung adenocarcinoma. Ceritinib is FDA approved as subsequent therapy for *ALK* + lung adenocarcinoma. As both are excellent options for treatment of *ALK*+ lung cancer, the trial will consist of two cohorts. The first will be for patients who have never been treated with an *ALK* inhibitor, the other will be for patients who have progressed on one *ALK* inhibitor.

1.6 Rationale for dose and regimen selection

The package insert for ceritinib recommends a starting dose of 750 mg daily. There are recommendations for dose adjustments for toxicity and renal/hepatic impairment. This dose has been associated with gastrointestinal toxicities often necessitating a dose reduction, In clinical practice, the starting dose is lower and side effects mitigated by the addition of food with the dose.

In a phase I study of Ceritinib 450 mg or 600 mg with a low fat meal was compared to 750 mg in ALK+ non small cell lung cancer. In this ASCEND-8 study, 137 patients were randomized to 750 mg daily with no food, 600 mg daily with food or 450 mg daily with food. The 750 mg dose patients showed similar

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steady state pharmacokinetics, while the 600 mg arm shows a 25% higher PK. The incidences of GI related AE's were lowest in the 450 mg arm with no grade 3 or 4 toxicities, while the remaining toxicities were similar. These data were presented in the Journal of Thoracic Oncology in 2017 (s1184, vol.12, No 1S).

2.0 Study Objectives

The hypothesis is that delivering SABR to patients with persisting tumors 10 weeks after ceritinib will result in superior overall tumor control, prolong PFS for patients and lengthen the duration of ceritinib activity in patients with *ALK*+ lung adenocarcinoma.

Published experience suggests that median PFS for patients who have previously been treated with crizotinib is less with ceritinib than those who have never been treated with crizotinib (7 months vs 10 months) (Shaw et al, NEJM 2014). As a result patients enrolled on this study will be divided into cohorts on the basis of prior exposure to crizotinib.

The primary endpoint of this study will be Progression-Free Survival (PFS); defined as time from initiation of ceritinib to evidence of disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

There may be progression in a specific localized region that is amenable to stereotactic radiation. If all existing lesions that enlarge and any new lesions that develop can still be effectively treated with stereotactic radiation, patients will be evaluated for repeat SABR therapy and ceritinib resumed. This will be at the recommendation of the treating physician according to standard practice. This will be defined as Time to 2nd SABR therapy and will be one of the secondary endpoints.

Similarly, if 3rd round of SABR can be safely provided with subsequent resumption of ceritinib, it will be defined as the Time to 3rd SABR therapy.

Cohort A (*ALK* inhibitor naive):

Primary Objective: To demonstrate the superiority of ceritinib combined with SABR in prolonging median PFS compared to historical control of 10 months

Primary Endpoint: Median PFS (as described in section 2.0) for study cohort, expected to be 20 months

Hypothesis: The addition of stereotactic radiation in patients with *ALK*+ lung adenocarcinoma receiving ceritinib will enhance efficacy leading to prolongation of time on ceritinib monotherapy.

Secondary Objectives: To describe overall survival in study participants
To describe the time to 2nd and 3rd SABR therapy
To determine the number of patients with CR, PR or stable disease by RECIST 1.1 criteria at 6 and 12 months

Secondary Endpoints: Overall survival
Time to 2nd SABR treatment, Time to 3rd SABR treatment

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PFS at 6 and 12 months from study initiation therapy

Safety Objectives: Demonstrate safety of ceritinib followed by SABR.

Safety Endpoints: toxicity and adverse events (CTCAE v.4)

Hypothesis: the safety of this combination of targeted therapy and radiation will be as safe as published experience of both these agents.

Cohort B (treated with one prior *ALK*-inhibitor):

Primary Objective: To demonstrate the superiority of ceritinib combined with SABR in prolonging median PFS compared to historical control of 7 months

Primary Endpoint: Median PFS (Time to subsequent systemic therapy) for study cohort, expected to be 14 months.

Hypothesis: the addition of stereotactic radiation in patients with *ALK*+ lung adenocarcinoma receiving ceritinib will enhance efficacy and prolongation of time on ceritinib monotherapy.

Secondary Objectives: To describe overall survival in study participants
To describe the time to 2nd and 3rd SABR therapy
To determine the number of patients with CR, PR or stable disease by RECIST 1.1 criteria at 6 and 12 months

Secondary Endpoints: Overall survival
Time to 2nd SABR treatment, Time to 3rd SABR treatment
PFS at 6 and 12 months from study initiation

Hypothesis: The combination of SABR and ceritinib will result in a clinically meaningful overall survival in study participants.

The early application of SABR will be effective in delaying progression which is amenable to SABR but does not require a change in systemic therapy

Safety Objectives: Demonstrate safety of ceritinib followed by SABR.

Safety Endpoints: toxicity and adverse events (CTCAE v.4)

Hypothesis:

The primary objective is to describe the PFS in patients undergoing study therapy. This is defined as evidence of disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

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Additional SABR to enlarging lesions will be permitted while on ceritinib, but no change in systemic therapy will be allowed. Patients who demonstrate oligo progression and have disease amenable to repeat courses of radiation therapy may resume ceritinib at the discretion of the treating oncologist until a change in systemic therapy is indicated.

The secondary objective of the study is to report overall survival and in *ALK*-positive lung adenocarcinoma. We will use Kaplan-Meier methods to estimate the overall survival.
The rate of overall response and its 95% confidence interval will be estimated using exact binomial method. Response duration will be summarized for patients who responded. Descriptive summary statistics like median, 25% and 75% percentiles will be used.

The secondary objective is also to describe the time to subsequent SABR in patients undergoing study therapy. Patients will be retreated with SABR if feasible. After the initial SABR to persisting lesions, if new lesions appear or if existing lesions enlarge but are amenable to SABR, patients will remain on study and listed as not having progressed. This time to 2nd and 3rd SABR will be recorded and reported. The secondary endpoint will be recorded as time to 2nd and (if applicable) 3rd SABR therapy.

The safety objective of this study to report the toxicity profile of the combination of ceritinib and SABR therapy. Both are well tolerated and routinely used in non-small cell lung cancer.

2.1 Translational and exploratory objectives

Radiation can potentially reverse tumor cell unresponsiveness in patients, even in sites that are have not been radiated. As noted above[17] (and in press), M1 and M2 macrophages play different roles in the tumor metastasis. ALK inhibition impacts the immunologic profile and potentially the subsequent development of metastases.

The exploratory objectives of this study would be to determine the impact of ALK inhibition and radiation on immune cell such as VEGFR2 expression, CD4/CD8 T-cells, NK cells and macrophages,. Blood will be collected at various time points during the study to determine any association with ceritinib or radiation.

2.2 Description of protocol design

This is an, open-label, two-cohort protocol designed to evaluate the activity of targeted therapy and SABR in *ALK*+ lung adenocarcinoma. Study participants will have to be eligible for both radiation and targeted therapy with ceritinib.

2.2.1 Treatment phase and duration of treatment

Patients eligible for treatment will receive 450 mg daily of ceritinib as part of a 28 day cycle. The first dose of each cycle will be administered after evaluation at the study center. Patients will remain on study and take ceritinib until there is evidence of disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason. In case of oligoprogression amenable to repeat courses of SABR, the treating oncologist may resume ceritinib if it is indicated per standard clinical practice. Patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments.

After 2 treatment cycles, lesions will be assessed by treating physician per RECIST 1.1. Persisting lesions will be treated with a course of SABR as feasible following at least 10 weeks of ceritinib treatment. Ceritinib will be held 3 days before the start of radiation. Patients will resume ceritinib 3 days

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after completion of the SABR. Regular surveillance will follow and any new or enlarging lesions that develop will be assessed for repeat SABR.

2.3 Definition of end of the Study

The study will end when all 33 patients have evidence of disease progression by RECIST1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

At the completion or discontinuation of study medication, all patients will be seen within 30 days for an end of therapy evaluation. This will include a safety assessment for AE's SAE's. Any unused medication will be returned.

2.4 Early Termination

Treatment on protocol may be terminated early if the Principal investigator or institution assess that the safety of the enrolled subjects will be compromised by continuation of the trial. The procedure followed will be that of the premature withdrawal patient and any patients on treatment will be seen as soon as possible.

3.0 Subject eligibility

3.1 Patient population

Subjects for this study will be selected from those with *ALK*+ lung adenocarcinoma. *ALK* analysis by Ventana or Vysis assay is routinely performed on lung adenocarcinoma to determine *ALK* status. Patients who are positive for an *ALK* rearrangement by gene sequencing will also be considered eligible for the study.

Patients will be informed about their potential eligibility status for this trial. None of these patients will be given any therapy or undergo any study related assessments/procedures until they have successfully screened and enrolled on to the therapeutic portion of the study.

Patients enrolled to the therapeutic portion of the study will have histologically proven lung adenocarcinoma with *ALK* abnormality detected by gene sequencing or assay as described above.

3.2 Inclusion criteria

Patients eligible for inclusion in this early treatment protocol have to meet **all** of the following criteria:

1. Histologically or cytologically confirmed diagnosis of lung adenocarcinoma that demonstrates *ALK* rearrangement as detected by the approved FISH test (Abbott Molecular Inc), using Vysis breakapart probes (defined as 15% or more positive tumor cells); or the Ventana IHC test. Evidence of rearrangement by gene sequencing tests such as FoundationOne or Caris will also be seen as evidence of *ALK* abnormality and meeting eligibility requirement.
2. Patients with no prior *ALK*-inhibitor therapy will be placed in cohort A, those treated with one prior line of *ALK*-inhibitor (at any time) will enter cohort B.
3. Patients will not have any other curative therapeutic option, such as radiation or surgery.
4. WHO performance status 0-2.
5. Age ≥18 years.
6. Patients must have recovered from all toxicities related to any prior anticancer therapies to ≤ Grade 2 (CTCAE v 4.03), provided that any concomitant medication is given prior to initiation of

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treatment with ceritinib. Exception to this criterion: patients with any grade of alopecia are allowed to enter the treatment.

7. Adequate organ function: the following laboratory criteria have been met:
   - Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L
   - Hemoglobin (Hgb) ≥ 8 g/dL
   - Platelets $\geq$ 75 x 10^9/L
   - Serum creatinine <1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥30 mL/min
   - Total bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with Gilbert's syndrome who may be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
   - Aspartate transaminase (AST) < 2.0 x ULN, except for patients with liver metastasis, who are only included if AST < 3 x ULN; alanine transaminase (ALT) < 2.0 x ULN, except for patients with liver metastasis, who are only included if ALT < 3 x ULN
   - Alkaline phosphatase (ALP) ≤5.0 x ULN
   - Fasting plasma glucose ≤175 mg/dL (≤9.8 mmol/L)
   - Serum amylase ≤ 2 x ULN
   - Serum lipase ≤ ULN

8. Patient must have the following laboratory values or have the following laboratory values corrected with supplements to be above the lower limit of normal before the first dose of ceritinib:
   - Potassium
   - Magnesium
   - Phosphorus
   - Total calcium (corrected for serum albumin)
9. Written informed consent for the protocol must be obtained prior to any screening procedures.
10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

3.3 Exclusion criteria

Patients eligible must not meet **any** of the following criteria:

1. Patients with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate).
2. History of carcinomatous meningitis.
3. Prior therapy with ceritinib.
4. Presence or history of a malignant disease other than lung adenocarcinoma that has been diagnosed and/or required therapy within the past year and is undergoing active anticancer treatment. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
5. Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
6. Patient who has received thoracic radiotherapy to lung fields ≤4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤2 weeks prior

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to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤2 weeks prior to starting study treatment is allowed.

7. Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as:
   - unstable angina within 6 months prior to screening;
   - myocardial infarction within 6 months prior to screening;
   - history of documented congestive heart failure (New York Heart Association functional classification III-IV);
   - uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication
     - initiation or adjustment of antihypertensive medication(s) is allowed prior to screening;
   - ventricular arrhythmias; supraventricular and nodal arrhythmias not controlled with medication;
   - other cardiac arrhythmia not controlled with medication;
   - Corrected QT (QTcF) >470 ms using Fridericia's correction on the screening ECG
8. Impaired GI function or GI disease that may alter absorption of ceritinib or inability to swallow up to five ceritinib capsules daily. Although, patients unable to swallow capsules will be allowed to participate in this study, by following the specific instructions on making a slurry of the medication.
9. Patient has impairment of GI function or GI disease that may significantly alter the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
10. Receiving medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with ceritinib and for the duration of participation (see Appendix 1 Tables):
    - Medication with a known high risk of prolonging the QT interval or inducing Torsades de Pointes (please refer to http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm)
    - Strong inhibitors or strong inducers of CYP3A4/5 (please refer to http://medicine.iupui.edu/flockhart/table.htm or http://www.druginteractioninfo.org)
    - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, CYP2C8 and/or CYP2C9 (please refer to http://medicine.iupui.edu/flockhart/table.htm or http://www.druginteractioninfo.org)
    - Therapeutic doses of warfarin sodium (Coumadin) or any other coumadin-derived anti-coagulant. Anticoagulants not derived from warfarin are allowed (eg, dabigatran, rivaroxaban, apixaban).
    - Unstable or increasing doses of corticosteroids; If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms (non-CNS), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment.
    - Enzyme-inducing anticonvulsive agents
    - Herbal supplements
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and agree to continue for 3 months after the last dose of study treatment. Highly effective contraception methods include:

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- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening) with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- Combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

13. Sexually active males unless they agree to use a condom during intercourse while taking drug and agree to continue for 3 months after the last dose of study treatment. Male patients for 3 months should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
14. Patient has a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.
15. Patient has other severe, acute, or chronic medical conditions including uncontrolled diabetes mellitus or psychiatric conditions or laboratory abnormalities that, in the opinion of the investigator, may increase the risk associated with study participation or may interfere with the interpretation of study results.
16. Patient has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study treatment or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can receive study treatment ≥1 week after these procedures.

4.0 Treatment Plan

4.1 Treatment Dosage and Administration

For this protocol, the term “treatment” refers to ceritinib. The dose and schedule are listed under table 4-1.

Each cycle of therapy will be 28 days long. A completed cycle will be 28 days of once daily continuous treatment. Day 1 will be the first day that ceritinib is taken, and the last day of a completed treatment

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cycle will be day 28. All doses prescribed to and taken by patients, any dose adjustments and interruption or discontinuations will be recorded in the clinical trial record.

Table 4-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ceritinib	Hard gelatin capsule for oral use	450 mg (3 x 150 mg capsule)	Once daily (28-day cycle)

4.1.1 Dosing regimen

Patients on this trial will begin therapy on day 1 of Cycle 1 with the first administration of ceritinib.

4.1.1.1 Ceritinib

Patients will self-administer the doses of ceritinib for the cycle.

Ceritinib will be administered orally once daily at a dose of 450 mg (3 capsules of 150mg ceritinib) on a continuous dosing schedule. The investigator must instruct the patient to take the ceritinib treatment exactly as prescribed.

- Patients should take ceritinib once daily at approximately the same time each day, in the morning, afternoon, or evening.
- Patients should take ceritinib with food.
- Each dose of ceritinib should be taken with a glass of water and consumed over as short a time as possible (i.e., not slower than 1 capsule every 2 minutes).
- For patients with a gastrostomy tube who are unable to swallow capsules, patient will be instructed on how to prepare mixture. For patients that are unable to swallow capsules, administration can occur through a nasogastric (NG) or gastric (G) tube:

1. Put on gloves and mask before opening containers. Take the appropriate number of capsules that are needed, out of the containers.
2. Place a glass bowl in an area with smooth surfaces that is easy to clean.
3. Carefully open each capsule, one at a time, and pour or tip the contents out of each capsule in the glass bowl.
4. Carefully check to make sure that both parts of each capsule are empty. Some of the contents may stick to the inside of the capsules. If this happens, use a toothpick (or similar tool) to remove the stuck contents into the glass bowl; work over the bowl.
5. Fill the glass bowl with at least 40 mL (eight teaspoons) of water. If taking a dose that is 200 mg or less, then use at least 20 mL (four teaspoons of water).
6. Mix the drug powder with water carefully with the spoon.
7. Put the end of the syringe in the glass bowl and slowly pull back on the plunger drawing the mixture into the syringe.
8. Make sure patient is sitting relatively upright, connect the syringe to the patient's NG or G-tube and empty the mixture by slowly pushing the plunger into the syringe until all contents are empty.
9. Repeat steps 7-8 if necessary, making sure the entire dose is administered.
10. Once the entire dose is given, rinse the tube by syringing in 20 mL (four teaspoons) twice. If dose is 200 mg or less, then use at least 10 mL (two teaspoons) of water twice for rinsing.
11. Dispose empty capsule shells, mask and gloves as per the hospital or institutions' guidelines

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

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Patients should be instructed not to make up missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 8 hours after the approximate time of the usual daily dosing. That day's dose (or partial remaining dose) should be omitted, and the patient should continue treatment with the next scheduled dose on the following day. The patient should record this in the medication diary.

4.1.2 Treatment duration

Patients will continue ceritinib treatment until they experience any of the following:

-Disease progression not amenable to SABR and necessitating change in systemic therapy determined by the treating physician.
-Unacceptable toxicity that precludes further treatment.
-Start of a new anti-cancer therapy.
-Pregnancy.
-Treatment is discontinued at the discretion of the investigator or patient.
-Lost to follow-up.
-Death.
-Completed.

4.2 Dose escalation guidelines

No doses escalation will be permitted on this study.

4.3 Dose modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the ceritinib treatment. Any changes in ceritinib administration will be recorded in the clinical trial record.

General guidelines for dose modifications

- For grade 1 and tolerable grade 2 treatment-related toxicities, patients are encouraged to continue at the current dose of study treatment. For intolerable grade 2 treatment-related toxicities, dosing should be interrupted until resolution to grade 1 or lower followed by dose reduction to the next dose level.
- For grade 3 or grade 4 treatment-related toxicity that is not considered by the investigator to be life-threatening, patients should interrupt study treatment until resolution to grade 1 or lower; then study treatment may continue following a dose reduction to the next dose level, if, in the opinion of the Investigator, the patient continues to experience clinical benefit. For any grade 3 or 4 treatment-related toxicity that is considered by the investigator to be life-threatening, permanently discontinue study treatment.

More detailed ceritinib dose modification guidelines are described in Section 4.3.1 respectively for selected toxicities.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria version 4.03.

Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater than 1 cycle (28 days)

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should be discontinued from ceritinib treatment unless the treating physician and Principle investigator agree that the patient should resume treatment.

All patients will be followed for safety until 30 days after the last dose of ceritinib.

4.3.1 Dose modification and dose delay of Ceritinib

Guidelines for dose interruptions and re-initiation of ceritinib treatment (with or without dose reduction) are described in Table 4-2. Dosing adjustment guidelines are in Table 4-3

Table 4-2 Dose reduction steps for ceritinib

Ceritinib dose levels	Dose* and schedule
Starting dose level	450 mg QD continuously
Dose level - 1	300 mg QD continuously
Dose level – 2**	150 mg QD continuously

*Dose reduction will be based on the worst preceding toxicity as per NCI-CTCAE version 4.03.

**Dose reduction below 150 mg/day is not allowed. If a dose reduction below 150 mg/day is required, the patient will be permanently discontinued from ceritinib.

Table 4-3 Criteria for interruption and re-initiation of Ceritinib treatment

Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for Ceritinib
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1.5 and ≥ 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 and ≥ 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a **single** temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓ 1 dose level

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Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for Ceritinib**
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75 and ≥ 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50 and ≥ 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
HEPATIC	
alkaline phosphatase and/or Gamma-glutamyl transpeptidase **(GGT)**	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct (conjugated) bilirubin only)	
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with liver function test (LFTs)*** monitored as per protocol
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from ceritinib
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from ceritinib
AST or ALT	
Grade 1 (> ULN and ≤ 3.0 x ULN)	Maintain dose level with LFTs*** monitored per protocol
Grade 2 (> 3.0 and ≤ 5.0 x ULN) without total bilirubin elevation to > 1.5 x ULN	Omit dose until resolved to ≤ Grade 1, then If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 5.0 and ≤ 20.0 x ULN) without total bilirubin elevation to > 1.5 x ULN	Omit dose until resolved to ≤ Grade 1, then If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
AST or ALT and concurrent Total Bilirubin	
AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue patient from ceritinib

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Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for Ceritinib
RENAL	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; > ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 and ≤3.0 x baseline; >1.5 and ≤3.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (>3.0 x baseline; >3.0 and ≤6.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from ceritinib
GASTROINTESTINAL	
Diarrhea**	
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level but adjust anti-diarrhea treatment (may change anti-diarrhea treatment)
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If diarrhea returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea***	
Grade 1 (despite standard anti-emetics)	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting***	
Grade 1 (despite standard anti-emetics)	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
METABOLIC	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose level
Hyperglycemia	

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Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for Ceritinib
Persistent hyperglycemia (glucose > 250 mg/dL despite optimal anti-hyperglycemic therapy)	Omit dose until hyperglycemia is adequately controlled then resume ceritinib at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management permanently discontinue patient from ceritinib.
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1	Maintain dose level
Grade 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves in ≤ 7 days, maintain dose level If grade 3 fatigue lasts > 7 days, omit dose until resolved to ≤ Grade 2 and then ↓ dose level
CARDIAC INVESTIGATIONS	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms)	Maintain dose level
Grade 2 (QTc 481-500 ms)	Maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	**When QTc ≥ 501 ms is identified at the site, interrupt ceritinib treatment and perform the following:** Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage for the potential to inhibit CYP3A4/5 and/or to prolong the QT-interval. Check compliance with correct dose and administration of ceritinib. **Perform a repeat ECG within one hour of the first QTc of ≥ 501 ms.** If QTc remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once a day until the QTc returns to < 501 ms. If QTc returns to ≤ grade 1 (< 481 ms), ceritinib will be reduced by 1 dose level (i.e., 600 mg QD or lower). **Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc < 481 ms**

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Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for Ceritinib
	Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms. If QTc of ≥ 501 ms recurs, interrupt ceritinib treatment. If QTc returns to ≤ grade 1 (< 481 ms), ceritinib may be reduced again by 1 dose level (i.e., 450 mg QD or 300mg QD). Repeat ECGs as described above. **If QTc of ≥ 501 ms recurs after 2nd dose reduction for QTc prolongation, the patient must be discontinued from study.** QTc of >480 ms should be reported as an adverse event (AE)
Grade 4 (QTc ≥ 501 or > 60ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from ceritinib
PULMONARY	
Notes: • Withhold ceritinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. • During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming ceritinib at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue patient from ceritinib.
BRADYCARDIA	
Grade 1	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of ceritinib
Grade 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of ceritinib
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If the concomitant medication can be adjusted or discontinued, resume ceritinib at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue ceritinib

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Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for Ceritinib**
PANCREATIC	
Amylase and/or lipase elevations (in the absence of clinical symptoms)	
Grade 1 (> ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥3 (> 2.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Note: Withhold ceritinib for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity. ** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator. ***LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), Alkaline phosphatase and GGT. **** Dose modifications apply to patients who experience diarrhea despite appropriate antidiarrheal medication. This medication should be started at the first sign of abdominal cramping, loose stools or overt diarrhea (see Section 4.3.2.5). ***** Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting (see Section 4.3.2.6).	

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4.3.2 Follow-up for toxicities

An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments (table 5-1).

Ongoing SAEs at the final safety evaluation visit or the end of study treatment visit (whichever is later) should be followed until they improve becoming non serious events, stabilize, or return to baseline levels. Refer to Section 7.2 for SAE.

A summary of selected toxicity follow-up recommendations is listed in table 4-4. For full toxicity information and dosing adjustments please refer to Table 4-3.

Table 4-4 Follow-up recommendations for specific toxicities

Toxicity	Follow-up evaluation*
Investigations (hematologic)	Febrile neutropenia, neutropenia or thrombocytopenia ≥ CTCAE Grade 3 Test weekly (or more frequently) until ≤ Grade 2 Subsequent monitoring must be performed every 3 weeks (or more frequently)
Investigations (hepatic)	Total ALT/AST/total bilirubin Grade 2: Test weekly (or more frequently) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 2 cycles (8 weeks). If no recurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks) Total ALT/AST/total bilirubin ≥ Grade 3: Test weekly (or more frequently) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 4 cycles (16 weeks). If no recurrence of ≥ grade 2 event, continue monitoring every cycle (4 weeks) Discontinuation due to liver toxicity: Test weekly (or more frequently) until ≤ Grade 1 or stabilization
Investigations (renal)	Serum creatinine Grade 2: Test weekly (or more frequently) until Grade 1 Thereafter, test every cycle (4 weeks) Serum creatinine ≥ Grade 3: Test twice weekly (or more frequently) until ≤ Grade 1 Thereafter, test every cycle (4 weeks)
Investigations (Metabolic)	Hyperglycemia ≥ Grade 3 Test weekly (or more frequently) until Grade 1
Investigations (pancreatic)	Amylase/lipase ≥ Grade 3: Test weekly (or more frequently) until ≤ Grade 1. After resumption of dosing, continue to test weekly for one additional cycle (4 weeks). If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks).

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*__Note__: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 4-3 for dose modifications required for applicable toxicities

4.3.2.1 Guidelines for the follow-up of laboratory hematologic abnormalities

In case of any occurrence of febrile neutropenia, neutropenia ≥ grade 3, or thrombocytopenia ≥ grade 3, hematology tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 2. Subsequent monitoring must be performed at least every 4 weeks.

4.3.2.2 Guidelines for the follow-up of laboratory liver abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include **ALL** of the following liver function tests (LFTs): albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase and GGT. Note: for patients with Gilbert Syndrome, total and direct bilirubin must be monitored, but intensified monitoring applies to changes in direct bilirubin only.

In case of any occurrence of ALT/AST/total bilirubin increase to grade 2 the LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Thereafter monitoring must be continued every 2 weeks (or more frequently if clinically indicated) for two additional cycles (e.g. 8 weeks). If there is no recurrence of ≥ grade 2 ALT/AST/total bilirubin elevations during this period, subsequent monitoring must be performed at least every 4 weeks.

In case of any occurrence of ALT/ AST/ bilirubin increase to grade 3 or 4, LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Thereafter monitoring must be continued every 2 weeks (or more frequently if clinically indicated) for four additional cycles (e.g. 16 weeks). If there is no recurrence of ≥ grade 2 ALT/AST/total bilirubin elevations during this period, subsequent monitoring must be performed at least every 4 weeks.

Patients who discontinue ceritinib treatment due to liver toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks).

4.3.2.3 Guidelines for the follow-up of laboratory renal abnormalities

In case of any occurrence of serum creatinine results of grade 2 or greater, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed at least every 4 weeks.

In case of any occurrence of serum creatinine ≥ grade 3, tests must be performed twice weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed at least every 4 weeks.

4.3.2.4 Guidelines for the follow-up of laboratory pancreatic abnormalities

In case of any occurrence of lipase or amylase increase to grade 3 or 4, both lipase and amylase must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 (or to baseline).

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After resumption of dosing, monitoring must be continued weekly (or more frequently if clinically indicated) for one additional cycle (i.e. 4 weeks). If there is no recurrence of ≥ grade 2 amylase or lipase elevations during this period, subsequent monitoring must be performed every 4 weeks.

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold ceritinib, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines descried in Table 4-3.

4.3.2.5 Guidelines for monitoring pneumonitis

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, withhold ceritinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD.

4.3.2.6 Guidelines for the treatment of study drug induced diarrhea

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004).

For example:

- For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered.
- For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms - moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.
- Dose adaptation of ceritinib in case of treatment related diarrhea must follow the guidelines presented above in the Criteria for interruption and re-initiation of ceritinib Treatment table.

4.3.2.7 Guidelines for the treatment of study drug induced nausea and vomiting

Nausea and vomiting are among the most frequently reported AEs following treatment with ceritinib and patients must therefore be closely monitored for the appearance of these AEs.

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g. discontinuation of

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concomitant medication, dietary modification, treatment of comorbidity). Adjusting the time of ingestion of ceritinib may influence perception and management of nausea (eg. taking it at bedtime).

Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In patients with vomiting, the patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment. For moderate emetogenic drugs, such as ceritinib, International Guidelines for anti-emetic treatment recommend early treatment with 5-HT3-receptor antagonists (5-HT3RAs).

- Dose adaptation of ceritinib in case of treatment related nausea and/or vomiting must follow the guidelines presented above in the Criteria for interruption and re-initiation of ceritinib Treatment table.

4.3.2.8 Guidelines for treatment of hypophosphatemia

Hypophosphatemia was not among the commonly reported AEs (i.e., < 15%), regardless of relationship to ceritinib treatment.

Therefore, phosphate levels should be checked at baseline and during treatment. In cases of hypophosphatemia at screening, phosphate supplements should be started and phosphate levels must be normalized before treatment is commenced with ceritinib. For any grade of hypophosphatemia during the study, treatment with phosphate supplements should be given as clinically indicated, and the ceritinib dose can be maintained.

4.3.3 Anticipated risks and safety concerns of the ceritinib treatment

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, e.g., diarrhea are provided in Section above. Refer to preclinical toxicity and or clinical data found in the Investigator's Brochure.

4.4 Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g., anti-emetics, anti-diarrheal agents) is permitted, except when specifically prohibited. The patient must be told to notify the investigational site about any new medications he/she takes after the start of the ceritinib treatment. All medications, including herbal/natural medications (excluding ceritinib treatment and prior antineoplastic treatments and blood transfusions), surgeries and procedures (including physical therapy) administered within 30 days prior to the first dose of administration of ceritinib treatment through 30 days after the last dose of ceritinib treatment will be recorded. Medications include not only physician prescribed medications, but also all over-the counter (OTC) medications, herbal medications (prohibited, see Section 4.4.2), food or vitamin supplements, and blood transfusions.

For up to date information on prohibited medications please refer to the following websites:

- Medication with a known High risk of prolonging the QT interval or inducing Torsades de Pointes (please refer to http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm)
- Strong inhibitors or strong inducers of CYP3A4/5 (please refer to http://medicine.iupui.edu/flockhart/table.htm or http://www.druginteractioninfo.org)

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- Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, CYP2C8 and/or CYP2C9 (please refer to http://medicine.iupui.edu/flockhart/table.htm or http://www.druginteractioninfo.org)

4.4.1 Permitted concomitant therapy requiring caution and/or action with ceritinib

4.4.1.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing ceritinib drug exposure to sub-therapeutic levels.

Systemic corticosteroid treatment must not be given during the study, except for stable doses of corticosteroid therapy such as dexamethasone and prednisone (e.g. for tumor associated symptoms) that are permitted during the course of the study. The corticosteroid dose must have been stabilized (or decreasing) for at least 5 days before initiating ceritinib therapy or 2 weeks when used for CNS related symptoms. High dose pulses of steroids are not allowed.

Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed.

Bisphosphonates

The use of bisphosphonates regardless of indication is allowed provided patients have been on stable doses for at least 4 weeks prior to the start of treatment. Patients requiring initiation of bisphosphonate treatment during the course of the study should be evaluated for progressive disease (result of evaluation should be clearly documented in the patient' source documentation) and will be subject to the same evaluation for stereotactic radiation to those areas. If the disease can be effectively controlled with radiation, initiation of bisphosphonates will be allowed. If bone involvement requires a change in systemic the patient will be recorded as having undergone progressive disease.

No drug-drug interaction is expected between LDK378 and bisphosphonates as the two drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of LDK378 and do not undergo metabolism *in vivo*.

The same guidelines apply to the use of denosumab for the treatment of bone metastatic disease

4.4.1.2 Drugs that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that the metabolism of ceritinib is mediated by CYP3A4/5. Ceritinib is a time-dependent CYP3A4/5 inhibitor and is also a potent reversible inhibitor of CYP2A6, 2B6, 2C8, 2C9 and 3A4/5 and may consequently increase exposure to drugs metabolized by these enzymes. Clinical studies have not yet been performed to confirm the potential effect of ceritinib onsubstrate drugs metabolized by these enzymes in patients. Also, the potential effect of low and moderate CYP3A4/5 inhibitors and inducers on ceritinib clearance is not known.

Concomitant treatment of ceritinib with weak inhibitors or inducers of CYP3A4/5 is permitted. Caution is advised when ceritinib is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5 (Appendix 1). Duration of concomitant treatment should be kept as short as possible, or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment. Note that co-administration of ceritinib with strong inducers or inhibitors of CYP3A4/5 is prohibited (Section 4.4.2.5).

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Concomitant treatment of ceritinib with medications known to be metabolized by CYP2A6, 2B6, 2C8 and 2C9 is allowed with caution (Appendix 1), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Section 4.4.2.6 and Appendix 1).

4.4.1.3 Non-enzyme inducing anti-epileptic drugs

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed.

4.4.1.4 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs; Appendix I) is allowed. However, PPIs should be used with caution due to the theoretical effects of long-acting pH elevating agents (i.e., prolonged acid suppression) on reducing ceritinib absorption. When the concurrent use of a H2-antagonist or an antacid with ceritinib is necessary, the H2 blocker must be administered 10 hours before or 2 hours after the ceritinib dose, and the antacid must be administered 2 hours before or 2 hours after the ceritinib dose. Time restrictions for the concurrent use of PPIs and ceritinib are not applicable due to the long-acting effects of PPIs on gastric pH (i.e., separation of doses will not likely impact this interaction).

4.4.2 Prohibited concomitant therapy with ceritinib

4.4.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy or biologic therapy, and anti-cancer surgery) other than the ceritinib treatment must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

The only radiation permitted will be SABR therapy given at the study institution as part of the trial. No other radiation will be allowed for patients.

4.4.2.2 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

4.4.2.3 Warfarin and coumadin derivatives

Warfarin sodium or any other coumadin-derivative anticoagulants are not permitted. Ceritinib is an inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible. Anticoagulants not derived from warfarin are allowed (eg, dabigatran, rivaroxaban, apixaban).

4.4.2.4 Enzyme inducing anti-epileptic drug (EIAED)

Use of EIAEDs is not permitted. Refer to Appendix 1 for a list of prohibited EIAED.

If a patient is currently taking an EIAED, he/she must have discontinued the EIAED therapy for at least 1 week prior to starting ceritinib treatment.

If a patient was previously on a non-EIAED and needs to permanently change anticonvulsant agent but cannot change to another non-EIAED, the patient will be taken off ceritinib.

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4.4.2.5 Strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of ceritinib is predominantly mediated by CYP3A4/5.

Strong inhibitors or inducers of CYP3A4/5 are prohibited. Patients receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. Refer to Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

4.4.2.6 Medications that are CYP2C8, CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index

Ceritinib is a potent inhibitor of drugs metabolized by the cytochromes CYP2C8, CYP2C9 and CYP3A4/5 *in vitro*. Because of the potential risk for drug-drug interactions, using medications known to be metabolized by these enzymes and that have a narrow therapeutic index is not permitted concomitantly with ceritinib. Refer to Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

4.4.2.7 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Patients should stop using herbal medications at least 7 days prior to first dose of ceritinib treatment.

4.4.2.8 Medications that may prolong the QT interval or have a known risk of inducing Torsades de Pointes

Ceritinib has potent activity on the hERG channel with an IC_{50} of 0.4 μM. However, there were no ceritinib-related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose (HED) of 1950 mg). Preliminary data from patients treated in the phase 1 study ([CLDK378X2101]) at doses of 50-750 mg suggest that ceritinib may have an effect on the QT interval. One patient (700 mg QD dose; <1%) had a QTc > 500 ms and 9 patients had an increase from baseline QTc > 60 ms.

Concomitant administration of ceritinib with drugs known to have a high risk of increasing the QTc interval and drugs known to increase the QTc interval that are also primarily metabolized by CYP3A4/5 should be avoided. Concomitant use of ceritinib and any medication included in Appendix 1 titled "List of prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a known risk of causing Torsades de Pointes) is not permitted.

4.5 Patient numbering, treatment assignment or randomization

4.5.1 Patient numbering

Each patient will be assigned a subject number at the time of screening which shall be the primary identifier for the patient throughout the entire trial. This number will not be reassigned if a patient is not enrolled on to the therapeutic portion of the trial. Once assigned a number, the patient will not be given a new number if enrollment is delayed behind other patients.

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4.5.2 Treatment assignment

Before the first dose of ceritinib, the investigator will confirm that the patient meets all eligibility criteria. The patient will be assigned to the treatment arm and the Investigator or delegate will update the trial record accordingly.

4.5.3 Treatment blinding

Not applicable.

4.6 Study drug administration

The investigator and delegates, as well as other study personnel will instruct the patient to take ceritinib according to protocol. This will only be after confirmation by the investigator or co-investigator that the patient is to continue and has received instructions on how to take the medicine per protocol.

For patients that are unable to swallow capsules, administration can occur through a nasogastric (NG) or gastric (G) tube:
1. Put on gloves and mask before opening containers. Take the appropriate number of capsules that are needed, out of the containers.
2. Place a glass bowl in an area with smooth surfaces that is easy to clean.
3. Carefully open each capsule, one at a time, and pour or tip the contents out of each capsule in the glass bowl.
4. Carefully check to make sure that both parts of each capsule are empty. Some of the contents may stick to the inside of the capsules. If this happens, use a toothpick (or similar tool) to remove the stuck contents into the glass bowl; work over the bowl.
5. Fill the glass bowl with at least 40 mL (eight teaspoons) of water. If taking a dose that is 200 mg or less, then use at least 20 mL (four teaspoons of water).
6. Mix the drug powder with water carefully with the spoon.
7. Put the end of the syringe in the glass bowl and slowly pull back on the plunger drawing the mixture into the syringe.
8. Make sure patient is sitting relatively upright, connect the syringe to the patient's NG or G-tube and empty the mixture by slowly pushing the plunger into the syringe until all contents are empty.
9. Repeat steps 7-8 if necessary, making sure the entire dose is administered.
10. Once the entire dose is given, rinse the tube by syringing in 20 mL (four teaspoons) twice. If dose is 200 mg or less, then use at least 10 mL (two teaspoons) of water twice for rinsing.
11. Dispose empty capsule shells, mask and gloves as per the hospital or institutions' guidelines

4.6.1 Study drug compliance

4.6.1.1 Study drug compliance

At each visit, the patient's compliance in study medication according to protocol will be assessed by the investigator and/or study personnel. This information will be entered into the Drug Accountability Form and captured into the source document at each visit, in their medication diary.

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5.0 Visit schedule and assessments

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for therapy on this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed.

For treatment on the trial, the patient must have a documented *ALK* abnormality either by sequencing or assay and meet the remainder of the eligibility criteria. This must be done at the treating center and all study required testing must be completed within the 30 day period prior to day of initiating therapy.

Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day).

5.1.2 *Medical history*

Complete medical and surgical history, history of infections

5.1.3 *Demographics*

Data to be collected on patient characteristics at screening include:

-Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

-lung adenocarcinoma diagnosis and extent of disease, including:

Date of diagnosis
Site of active disease
Prior antineoplastic therapies (medications, radiation, surgeries)
Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 30 days before the first dose of ceritinib treatment is administered will be noted in the clinical trial medication record and updated on a continual basis if there is new change to the medication.

5.1.4 *Review subject eligibility criteria*

According to section 3

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5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status*

Performance status evaluated prior to study entry

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 7.1 for Adverse Event monitoring and reporting.

5.1.9 *Hematology*

Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))

5.1.10 *Serum chemistries and coagulation*

Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, glucose, phosphate (inorganic phosphorus), alkaline phosphatase, GGT, lipase, amylase. Creatinine clearance will be calculated using the serum creatinine value. Coagulation tests will be Prothrombin Time (PT) and Partial Thromboplastin Time.

5.1.11 *Immune profile*

M1/M2/VEGFR2 macrophages, NK cells, CD4/CD8 ratio, ALK in immune cells and others

5.1.12 Urinalysis

Macroscopic panel (dipstick)(color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)

Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)

5.1.13 ECG

A standard 12 lead ECG should be used for assessments.

5.1.14 *Pregnancy test (for females of child bearing potential)*

At screening visit, serum pregnancy test will be performed. Following the screening assessment, urine pregnancy tests should be performed.

5.1.15 *Tumor assessment*

To be performed using radiographic imaging according to section 5.3.1.

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5.1.16 Follow-up after Treatment

The study team will attempt to collect survival status and new therapy information for patients who are enrolled. Public sources may be searched for survival status information.

5.2 Protocol flow and visit schedule

Table 5-1 lists the protocol schedule and assessments and indicates when particular assessments will be performed with an “X”. The cycle length is fixed at 28 days, and will be maintained regardless of whether there were dose modifications or interruptions in therapy. If treatment with ceritinib is interrupted, future visits and assessments will continue as listed from cycle 1 day as Day#1 for the purpose of scheduling. Screening procedures may overlap with Cycle 1 Day 1 procedures only if all eligibility criteria is met and confirmed prior to dosing. A physician visit is not needed on C1D1 if performed within 7 days prior to starting treatment. In this case, delegated study personnel may assess performance status (WHO) on Cycle 1 Day 1.There will be variation of up to +/- 3 days allowed in visits and assessments. A delay of Cycle Day 1 for subsequent cycles beyond cycle 2, due to holiday, inclement weather, or other unforeseen circumstances will be permitted for a maximum of 7 days.

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Table 5-1 Visit evaluation Schedule	**Protocol Section**	***ALK* abnormality**	**Screening / Baseline**	**Day 1 of Cycle 1 (28d) +/-3**	**Day 15 of Cycle 1 (28d) +/-3**	**Day 1 of Cycle 2 (28d) +/-3**	**Day 1 of Subsequent cycles (28d) +/-3**	**End of study treatment (EoT) (at last visit, or up to 30 days**	**Long Term Follow up Q3 mo following EOT**
Visit Number			**1**	**2**	**3**	**4**	**5, 6..**	**Last**	
Day of cycle		**-180 to -1**	**-30 to -1**	**D1**	**D15**	**D29**	**D57, D85..**	**Last**	
Obtain Informed Consent	ICF	X	X						
Patient history									
Inclusion/exclusion criteria	3.2 & 3.3		X						
Documentation of *ALK/* positivity by sequencing, FISH or IHC	5.1.1	X	X						
Diagnosis and extent of cancer	5.1.2		X						
Demography	5.1.3		X						
Relevant medical history/current medical conditions	5.1.4		X						
Prior antineoplastic therapy (meds, surgery, radiation)	5.1.5		X						
Prior/concomitant medications	5.1.5		X	Continuous					
Surgical and Medical Procedures	4.4		X	Continuous					
Eligibility Screening	5.1.4		X						
End of Phase Disposition	5.1.1.1 and 5.1.3		X Screening Phase Disposition					X End of Treatment Phase	
Physical examination	**5.1.6**		**X**			**X**	**X**	**X**	
Performance status (WHO)	5.1.7		X	X			X	X	
Height	5.1.6		X						
Weight	5.1.6		X	X		X	X	X	
Vital signs	5.1.6		X	X		X	X	X	
Survival Assessment	5.1.16								X

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Table 5-1. Visit evaluation Schedule (continued)	**Protocol Section**	***ALK* abnormality**	**Screening / Baseline**	**Day 1 of Cycle 1 (28d) +/- 3**	**Day 15 of Cycle 1 (28d) +/-3**	**Day 1 of Cycle 2 (28d) +/- 3**	**Day 1 of Subsequent cycles (28d) +/- 3**	**End of study treatment (EoT) (at last visit, or up to**	**Long Term Follow Up Q3 mo following EOT**
Visit Number			**1**	**2**	**3**	**4**	**5, 6,…**	**Last**	
Day of cycle		**-180 to -1**	**-30 to-1**	**1**	**D15**	**D29**	**D57, D85..**	**Last**	
Lab assessments*			X	X *	X	X	X	X	
CBC	5.1.9		X	X	X	X	X	X	
Chemistry, lipase, amylase	5.1.10		X	X	X	X	X	X	
Coagulation	5.1.10		X						
Creatinine clearance	5.1.10		X		X				
Urinalysis (dipstick) with microscopic analysis	5.1.12		X		X			X	
Immune profile/correlatives,	5.1.11			X	X		X(Cycle 3 and 6 only))	X	
circulating biomarker levels, resistance markers, CTC biomarker analysis	5.1.11			X	X		X (Cycle 3 and 6 only)	X	
Pregnancy test	5.1.14		X			X	X	X	
Imaging									
Standard of care imaging of neck/chest/abdomen (CT, MRI) as indicated to areas of known/ suspected disease	5.2.1		X				X (Every 2 cycles or 8 weeks)		
Standard of Care Imaging of the brain as clinically indicated (MRI/CT)	5.2.1		X (if known or suspected brain metastases)				X (every 12 weeks or 3 cycles)		
Safety									
Adverse events	7.1		X	Continuous					
ECG	5.1		X	X		X	X (Every even cycle)	X	
Drug administration	**4.1**			**Continuous**					

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* Baseline laboratory assessments must be performed on Cycle 1 Day 1 or within 24 hours prior to dosing.

- Please refer to Table 5-3 for local Clinical laboratory parameters

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5.2.1 Screening/Baseline

Screening assessments to confirm eligibility will be performed as per the schedule of assessments. Documented Informed consent must be obtained before any study specific procedure will be performed.

The patient must have a documented *ALK* abnormality either by sequencing or assay and meet the remainder of the eligibility criteria. All study required testing must be completed within the 30 day period prior to day of initiating therapy.

Re-screening of patients will be allowed, if all entry criteria are met during the re-screening phase time period (-30 days to -1 day).

5.2.1.1 Biomarker required for Eligibility on this trial arm

Patient eligibility will be checked once all screening procedures are completed.

5.2.1.1.1 *ALK* positivity

Histologically or cytologically confirmed diagnosis of lung adenocarcinoma with *ALK* positivity will be required to be considered eligible for the therapeutic portion of the trial. *ALK* testing will be via:

i. FISH test for *ALK* rearrangement using the FDA-approved FISH test (Abbott Molecular Inc), using Vysis breakapart probes (defined as 15% or more positive tumor cells). or

ii. *ALK* positivity by protein expression, as determined by positive immunohistochemistry (IHC) assay. or

iii. Next generation sequencing using a CLIA certified laboratory demonstrating positivity for *ALK* translocations.

Documentation of *ALK* positivity using one of the above tests is required.

5.2.1.2 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

-Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

-Relevant medical history

-lung adenocarcinoma diagnosis and extent of disease, including:

- Date of diagnosis
- Site of active disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 30 days before the first dose of ceritinib treatment is administered will be noted in the clinical trial medication record and updated on a continual basis if there is new change to the medication.

5.2.1.3 Information to be collected on screening failures

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The reason for not entering the treatment protocol will be recorded. The demographic information, informed consent, and Inclusion/Exclusion pages will be completed for Screen Failure patients. No other data will be entered into the clinical database for patients

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who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 7 for SAE reporting details).

Subjects who signed ICF but are considered ineligible after signing the study consent will be considered as screening failures, and data will be handled in the same manner.

The following information will be recorded for screening failure patients:

-Screening Phase Disposition page (including reason for not satisfying eligibility criteria and being started on treatment).
-Informed consent.
-Demography.
-Adverse Events (only if an SAE occurs).
-Inclusion/Exclusion Criteria.

5.2.2 Treatment period

Following completion of screening procedures and verifying patient eligibility, the patient will be approved for treatment per protocol.

The study treatment phase begins on Cycle 1, Day 1 with the first administration of ceritinib and will continue to receive ceritinib treatment until disease progression by RECIST1.1 not amenable to SABR necessitating a change in systemic therapy, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason whichever occurs first. Patients who have RECIST-defined PD as assessed by the investigator but who, in the opinion of the investigator, have evidence of continued clinical benefit from ceritinib may continue to receive the study medication upon approval by the principal investigator. In such cases, these patients must continue to be followed for safety and efficacy assessments as per the schedule of assessments. Patients will be assessed as per visit schedule in Table 5-1.

There is a visit windows of ± 3 days for scheduled study assessments.

5.2.3 End of treatment visit including study completion and premature withdrawal

5.2.3.1 End of Phase Disposition

Patients will be evaluated upon discontinuation of the ceritinib by a clinic visit. At that time all assessments listed for End Of Treatment will be performed. A note will be entered into the clinical trial record will be completed, giving the date and reason for stopping the ceritinib treatment.

At a minimum, all patients who discontinue ceritinib treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of treatment.

5.2.3.2 Criteria for patient withdrawal

Patients may voluntarily withdraw from the study (no further study data to be collected) at any time.

Patient death will be considered as a withdrawal from the study. Patients may also be withdrawn (the physician may decide to remove the patient from any further study activity) if any of the following occur:

- Adverse event(s) (see Section 7.1)
- Disease progression
- Major protocol deviation
- Technical problems
- Physician decision

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- Non-compliance with study treatment.
- Death
- Completed

Patients must be withdrawn if any of the following occur:

- Lost to follow-up
- Subject/guardian decision
- Pregnancy (Pregnancy will be followed for outcome)

Patients lost to follow up should be recorded as such in the clinical trial record. For patients who are lost to follow-up, the investigator will record the attempts at “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

5.2.3.3 Replacement policy

If an eligible patient is unable to start therapy with ceritinib, they may be replaced with another eligible patient if they have not received any study drug.

Apart from the above, patients will not be replaced on this study.

5.3 Assessment types

5.3.1 Efficacy assessments

Efficacy evaluations will be via revised RECIST 1.1 criteria on imaging performed at the conclusion of every 2 cycles. Target lesions will be identified prior to initiation of therapy on imaging and will be followed on subsequent imaging.

Physical exam findings of progressive disease will be considered as sufficient for documented progression if the record records biopsy proven tumor measurements in 2 dimensions and shows an increase in both dimensions of 20%. If the progression is amenable to SABR, the patient will receive SABR and be maintained on ceritinib. If the progression is not amenable to SABR and a change in systemic therapy is needed, the patient will be considered to have progressed and have reached the end of the study.

Imaging exams will be according to standard of care guidelines to areas of known/suspected disease. These will include CT of the neck, chest, abdomen and pelvis as well as MRI of the brain. Other tests may be clinically indicated, these will be ordered according to disease and patient specific guidelines. Imaging of the brain will be performed at baseline by CT or MRI per standard of care for lung adenocarcinoma.

Subjects with known CNS metastases must have an MRI of the brain performed every 3 cycles while on study. If an MRI cannot be performed, CT of the brain would be an acceptable alternative. Subjects without documented CNS metastases will not have mandated CNS imaging requirements.

5.3.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 7. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

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5.3.2.1 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. Information about the physical examination will be present in the source documentation. For the assessment schedule refer to Table 5-1.
Significant findings that were present prior to the signing of informed consent must be included in the clinical trial record. Significant new findings that begin or worsen after informed consent must be recorded in the clinical trial record.

5.3.2.2 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements. Blood pressure (systolic and diastolic) and pulse should be measured.

For the assessment schedule refer to Table 5-1.

5.3.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only.
For the assessment schedule for weight refer to Table 5-1.

5.3.2.4 Performance status

WHO performance status will be assessed as per the assessment schedule (refer to Table 5-1). Assessment of WHO performance status (Table 5-2) will be performed within the time windows described above of the scheduled assessment, even if ceritinib medication is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 5-2 WHO Performance status scale

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.3.2.5 Laboratory evaluations

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry, urine, and other blood specimens collected as part of safety monitoring. All unscheduled blood testing will be performed locally, with exceptions for emergency conditions. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 5.1).
Laboratory abnormalities that are considered clinically significant, induce clinical signs or

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symptoms, require concomitant therapy or require changes in ceritinib treatment constitute an adverse event (AE) and must be reported as an AE in the clinical trial record.
Laboratory values obtained at the screening visit will be used to assess eligibility to meet inclusion criteria. In addition, eligible patients must have baseline laboratory assessments performed on Cycle 1 Day 1 or within 24 hours prior to dosing.

5.3.2.5.1 Hematology
Hematology assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

Table 5-3 Local Clinical laboratory parameters collection plan

Test Category	Data Results	Test Name
Hematology		Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))
Chemistry		Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, glucose, phosphate (inorganic phosphorus), alkaline phosphatase, GGT, lipase, amylase
Coagulation		PT/PTT
Creatinine clearance		Creatinine clearance
Urinalysis		Macroscopic panel (dipstick)(color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Pregnancy test		For women of childbearing potential : At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test. If local requirements dictate otherwise, local regulations should be followed

5.3.2.5.1 Hematology
Hematology assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

5.3.2.5.2 Clinical chemistry and Creatinine clearance
Clinical chemistry and Creatinine clearance assessments of the parameters listed in Table 5-3 will be tested as per the schedule of assessments (Table 5-1).

5.3.2.5.3 Urinalysis
Dipstick measurements will be performed as per Table 5-3 and according to the schedule of assessments (Table 5-1). Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 5-3.

5.3.2.5.4 Pregnancy and assessments of fertility
During screening, a serum pregnancy test will be completed. Starting on day 1 of Cycle 2, and at EOT, urinary pregnancy test (dipstick) will be performed. The time windows granted for pregnancy testing are

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identical to the corresponding visit time windows for each visit. If local requirements dictate otherwise, local regulations should be followed.

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit.

If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

5.3.2.6 Translational analysis

To analyze the immunologic impact of SABR and ceritinib, 16 ml of whole blood (8ml X 2 tubes) will be drawn from patients into BD Vacutainer Whole Blood Tube, ACD A, (Yellow, 8.5 mL), at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 and Cycle 6 day 1, and end of treatment.

For circulating ALK biomarker and resistance mechanism analysis, 30 ml of whole blood (10 X 3 tubes) will be drawn into Streck CELL-FREE DNA BCT® at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 and Cycle 6 day 1, and end of treatment. Plasma will be processed and frozen for ALK and resistance mechanism analysis. CTCs will be enriched and captured and interrogated for biomarker analysis.

Blood will not be drawn if the investigator is concerned that doing so may harm the patient.

5.3.2.7 Cardiac assessments

5.3.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG should be used for assessments.
All ECGs will be performed locally and reviewed by investigator prior to ceritinib treatment administration. Please refer to Table 5-4 for cardiac assessment monitoring schedule.

Table 5-4 ECG collection plan

Cycle	**Day of cycle**	**ECG monitoring[a]**
	Screening[b]	1 single ECG
Cycle 1	1	Pre-dose: 3 sequential ECGs separated by at least 2-4 minutes
Cycle 2	1	Pre-dose: 1 single ECG
Even numbered cycles (4,6,8…)	1	Pre-dose: 1 single ECG
EOT	N/A	1 single ECGs recorded

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[a] Refer to Table Criteria for interruption and re-initiation of ceritinib treatment for the recommended dose modifications due to QTc interval prolongation
[b] The screening ECGs will be reviewed by investigator for eligibility of the patient. (Note: the mean QTc interval at baseline must be ≤ 450msec for the patient to be eligible for participation in the trial)
Note: Additional monitoring performed at the Investigator's discretion, if medically indicated.

Interpretation of the tracing must be made by a qualified physician and documented. Clinically significant abnormalities present when the patient signs the informed consent should be reported. New or worsened clinically significant findings occurring after informed consent must be recorded.

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study drug.

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

6.1.2 Disease Parameters

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

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target

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lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

CT scans of the neck, chest, abdomen and pelvis will be performed at baseline and every two cycles according to standard of care. Other imaging of these areas such as PET/MRI will be allowed if CT cannot be performed. MRI of the brain will be performed at baseline and as clinically indicated. Wherever it can be safely given, radiographic contrast agents should be given for the imaging studies.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

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Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

Note: Subjects 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.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

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6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that:
i. recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) AND is amenable to SABR. This will be defined as time to subsequent SABR.
ii. recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) and is NOT amenable to SABR. This will be defined as progression on systemic therapy.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

6.1.6 Progression-Free Survival

Progression Free Survival will be the primary endpoint for this study. If oligoprogression occurs that is amenable to repeat treatment with SABR, the ceritinib will be held and SABR therapy delivered. If the treating oncologist then feels the patient would benefit from continuing the ceritinib that will be permitted. The patient will however be have been deemed as having progressed even if ceritinib is resumed.

After the initial SABR to persisting lesions if new lesions appear or if existing lesions enlarge but are NOT amenable to SABR (necessitating a change in systemic therapy), the patient will have completed the therapeutic portion of the study.
Time to 2nd SABR is defined as the duration of time from the start of treatment to the time of development of new or enlarging lesions that are amenable to SABR and the progression does not require a discontinuation of ceritinib.

Time to 3rd SABR is defined in patients who have already received two rounds of SABR while on this study as the duration of time from the start of treatment to the time of development of new or enlarging lesions that are amenable to SABR and the progression does not require a discontinuation of ceritinib.

7.0 Adverse events

7.1.1 Contraindications:

Known allergy to ceritinib, no specific contraindications listed in package insert.

7.1.2 Special Warnings and Precautions for Use:

Cardiac: symptomatic bradycardia can occur with heart rate <50/min. If possible, will avoid concurrent use of agents that may cause bradycardia (eg, beta blockers, nondihydropyridine calcium channel blockers, clonidine, digoxin). Will monitor heart rate and blood pressure regularly. Dose will be held for symptomatic bradycardia.

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QTc prolongation: QTc interval prolongation has occurred in clinical studies, and may be concentration-dependent. Will periodically monitor ECG and electrolytes in patients with heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications known to prolong the QTc interval. May require treatment interruption, dosage reduction, or discontinuation. Will permanently discontinue in patients who develop QTc interval prolongation in combination with torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Gastrointestinal toxicity: Diarrhea, nausea, vomiting, or abdominal pain occurred in the majority of patients in clinical trials; over one-third of patients required dose reductions due to severe or persistent gastrointestinal toxicity. Symptomatic management will be with antiemetics and antidiarrheals.

Hepatotoxicity: Hepatotoxicity has been observed in patients treated with ceritinib in clinical trials, including ALT levels >5 times ULN in over one-quarter of patients.

Hyperglycemia: Hyperglycemia, including grade 3 and 4 toxicity, has been observed in ceritinib-treated patients. Close monitoring of blood sugars in patients with baseline random blood sugar greater than 180, with addition of insulin or other medication to correct hyperglycemia.

Pulmonary toxicity: Severe and life-threatening interstitial lung disease (ILD)/pneumonitis (some fatal) may occur. Monitor for signs/symptoms of pulmonary toxicity; permanently discontinue in patients diagnosed with treatment related ILD/pneumonitis.

7.1.3 Interaction with other medications

CYP3A inducers and inhibitors: these should be avoided while patients are receiving ceritinib. If a strong CYP3A inhibitor must be given concurrently, the dose of ceritinib should be reduced. Similarly concurrent administration of substrates of CYP3A and CYP2C9 should also be avoided.

Please note Section 14.1 for a full list of medications that require caution.

7.1.4 Adverse Reactions

In the dose escalation phase patients were treated on a once daily schedule at the following dose levels: 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg and 750 mg. The MTD was determined to be 750 mg daily. Following determination of the MTD in May-2012 the expansion part of the study opened at the 750 mg daily dose level.

During the dose escalation part of the study, first cycle dose-limiting toxicities (DLTs) that contributed to the definition of the MTD included hypophosphatemia (400 mg), ALT elevation (400 mg), nausea with dehydration (600 mg), diarrhea (600 mg and 750 mg), and vomiting (750 mg). There were 3 cases of grade 3 hypophosphatemia, one of which was a DLT that contributed to the MTD determination – this patient was able to continue ceritinib at the same dose. In all cases patients were able to continue therapy without dose modification. Hypophosphatemia was not among the most commonly reported AEs (i.e., < 10%), regardless of relationship to ceritinib treatment.

The majority of adverse events, regardless of relationship to study drug, have been Grade 1-2, and have not required dose interruption or reduction. The most common adverse events were gastrointestinal toxicities, including nausea, diarrhea and vomiting, occurring in 72.7%, 72.7%, and 55.5% of patients, respectively. Other adverse events occurring in more than 20% of patients included fatigue (30.9%), abdominal pain (27.3%), decreased appetite (25.9%), ALT increased (25.0%) and constipation (21.4%). Grade 3 and 4 adverse events were much less common, with none occurring in 16% or more of patients. ALT increase, AST increase and diarrhea were the most common grade 3 or 4 events, occurring in

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15.5%, 7.3% and 5.9% of patients, respectively. All other grade 3 or 4 events occurred in less than 5% of patients.

Preliminary ECG data from 220 patients treated at doses of 50-750 mg suggest that ceritinib may have an effect on the QT interval. One patient (700 mg QD dose; <1%) had a QTc > 500 msec and 2 (1.6%) patients (1 at 700 mg QD dose, 1 at 750 mg QD dose) had an increase from baseline QTc > 60 msec.

Interstitial lung disease/pneumonitis has been reported in some patients treated with ceritinib. Five cases improved or resolved with interruption of ceritinib and treatment with antibiotics and/or steroids. In one case, ceritinib was resumed at a reduced dose without recurrence of pneumonitis. Recurrent pneumonitis has also been reported following re-challenge of cases at a lower dose of ceritinib. Two fatal outcome of treatment-related pneumonitis has been reported.

In summary, ceritinib has been generally well tolerated by patients with *ALK*-rearranged NSCLC at doses up to the MTD of 750 mg daily. GI toxicities are common, but they are generally grade 1-2, and resolve with holding ceritinib and reducing the dose in the setting of grade 3-4 events.

7.2 Adverse Event Monitoring

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

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

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death

7.2.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research. Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

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Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study. Refer to the UTSW IRB website at http://www.utsouthwestern.net/intranet/research/research-administration/irb/study-management/adverse-events.html to determine when a serious adverse event requires reporting to the IRB.

Unanticipated Problems

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely, probably, or possibly related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.2 Reporting

Local unanticipated problems require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix IV of the SCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB in not required).*

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All local serious adverse events which occur on research subjects on protocols for which the SCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on this clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating staff are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

	Telephone reports to: (Investigator: Sawsan Rashdan, office # 214 6484180, pager 972-229-3813) UTSW SCC Data Safety Monitoring Committee Coordinator (if fax report is not available) within 2 working days to 214-648-7097.
	Written reports to: (Investigator: Sawsan Rashdan, office fax # 214 6481955, 5323 Harry Hines Blvd, Dallas, TX 75390-8852) UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-7018 or deliver to NB 2.418 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

7.2.2.1 SAEs

Local serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped LDK378 treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAE experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the LDK378 treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the

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completed, signed form by FAX (1-877-778-9739) within 24 hours of learning of its occurrence along with Novartis SAE Report Fax Coversheet to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis LDK378 treatment, an oncology Novartis DS&E department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees (EC) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.2.2.2 Unanticipated Problems

Local unanticipated problems require reporting to the UTSW IRB within 2 working days of PI awareness of the event.

Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

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Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.3.1 Laboratory test abnormalities

7.3.1.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in ceritinib treatment), should be record. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

7.3.2 Adverse events of special interest (AESI)

Adverse events of special interest to be monitored for ceritinib have now also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations).

7.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis immediately (within 24 hours) of learning of its occurrence. Patients who become pregnant during the trial must be withdrawn. The pregnancy will be followed up from the estimated date of delivery plus 3 months to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment. A pregnancy outcome informed consent will be provided by Novartis. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 3 months after treatment has been stopped.

If a pregnancy occurs while on LDK378 treatment, the newborn will be followed for at least 3 months.

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7.5 Warnings and precautions

Additional safety information collected between IB updates will be noted and added to the protocol. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. The package insert for ceritinib does not contain any specific contraindication.

8.0 Study agents and therapies

8.1 Agent Ceritinib

- Other names for the drug(s): Ceritinib, Zykadia, LDK378
- Classification - type of agent: Targeted cancer therapy
- Mode of action: *ALK* inhibitor
- Storage and stability: should be stored at 25 C, with a range of 15-30C.
- Protocol dose: 450 mg
- Preparation: 150 mg Hard gelatin capsule
- Route of administration for this study: Oral
- Incompatibilities: none
- Availability: FDA-approved
- Side effects: Please refer to the ceritinib package insert for a comprehensive list of adverse events.

Commonly reported adverse events include Gastrointestinal symptoms such as diarrhea, nausea and vomiting, anorexia, and constipation. Fatigue is also commonly reported. Decreased hemoglobin and serum phosphate, increased serum glucose, ALT and bilirubin have also been reported. Cardiovascular side effects include bradycardia and prolonged Q-T interval on ECG. Visual disturbances and interstitial pulmonary disease have also been reported.

- Nursing implications: none

8.1.1 Return and Retention of Study Drug

The study drug ceritinib will be destroyed by the UT Southwestern designated investigational drug service pharmacy in accordance with institutional protocols. No patient returned drug will be re-assigned to other patients or diverted to another person.

8.1.2 Study Drug compliance

The patient will be asked to keep a diary of taking the medication, as well as bringing pill bottles to each clinic visit.

8.2 Therapy Stereotactic Ablation Body Radiation (SABR)

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8.3 SABR DOSE AND TECHNIQUES

SABR will begin 10 weeks after initiation of ceritinib for consolidation of residual disease sites. Additional SABR treatments will be delivered to new distinct areas of disease that develop after that period at the discretion of the treating medical oncology/radiation oncology teams. PFS will at that point already been established, but patients will be followed for OS.
Stereotactic treatment is the targeting, planning, and directing of treatment fields guided to a target based on known 3-D coordinates related to reliable fiducial markers. This differs from conventional radiation therapy in which treatment is guided by skin or bony landmarks assumed to correlate to the target volume based on the initial simulation. SABR in this study will be delivered with an ablative range of dose per fraction. Treatment will account for inter/intra-fractional errors with careful dosimetry that delivers an ablative dose to the metastatic lesion(s) while respecting normal tissue constraints.

8.3.1 Ceritinib during SABR

It is not expected ceritinib and SABR would have significant toxicity if given concurrently. However to minimize risk to the patient, ceritinib will be held for 72 hours before the first radiation treatment and resumed 72 hours after the last radiation dose. While radiation is being delivered, concurrent treatment with ceritinib is not allowed.

8.3.2 SABR Prescription

Patients randomized to the SABR arm will be evaluated by the treating Radiation Oncologist. Based on location of the metastatic lesion(s), dose fractionation will be determined by clinical appropriateness that balances ablation of the lesion(s) while respecting normal tissue constraints.

Prescription Dose

	Total Cumulative Dose Encompassing 95% of Planning Target Volume		
Number of Fractions	Protocol Compliant	Variation Acceptable	Deviation Unacceptable
1	21-27 Gy	<21 Gy but ≥16 Gy	<16 Gy or >27 Gy
3	26.5-33 Gy	<26.5 Gy but ≥24.5 Gy	<24.5 Gy or >33 Gy,
5	30-37.5 Gy	≥28 Gy, <30 Gy	<28 Gy or >37.5 Gy,

Treatment may be delivered on consecutive days with 18 hours between fraction or every other day as deemed appropriate by the treating Radiation Oncologist.

If there is residual disease not amenable to SABR fractionation schemes proposed in the study, especially for bulky hilar or mediastinal disease, a fractionation schema of 45 Gy in 15 fractions may be employed, with adherence to standard normal tissue constraints outlined in the trial. This treatment will be delivered daily for three weeks.

8.3.3 Planning Constraints and Concerns

The tolerance dose of SABR to the gastrointestinal tract is not established, and patients with metastatic disease involving the esophagus, stomach, intestines, or mesenteric lymph nodes will not be eligible. Patients with renal or adrenal metastases are potentially eligible if normal tissue constraints are otherwise met.

Cutaneous metastases are an uncommon manifestation of non-small cell lung cancer that are typically associated with poor prognosis [22] . Patients with cutaneous metastases will be ineligible. As this may represent a group of patients with particularly poor prognosis, again this will be considered within any comparison with historical controls.

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It is well established that for palliative effect for a painful bone metastasis, a single dose of 8 Gy is usually as effective as 30 Gy. Long term survival after bone metastasectomy has been reported [23]. Irradiation of non-spinal skeletal sites does not generally require specialized techniques of treatment. Metastases in major lower extremity weight-bearing bones should undergo surgical stabilization if there is plain film evidence of cortical erosion.

Corticosteroid premedication will not be mandated, although it can be used at the discretion of the treating oncologist. Analgesic premedication to
avoid general discomfort during long treatment durations is recommended when appropriate.

8.4 Technical Factors

8.4.1 Physical Factors

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-15 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Restriction of photon beam energies > 10 MV but less than 15 MV will be based on clinical appropriateness taking into account distance the beam must travel to the target.

8.4.2 Dose Verification at Treatment

In-vivo dosimeter measurements (e.g., diode, TLD) may be obtained for surface dose verification for accessible beams. This information is not required by the protocol.

8.4.3 Treatment Platforms

The trial allows most commercially available photon producing treatment units except the exclusion of units described in Section 4.3.1 (e.g., cobalt units and charge particle accelerators). Conventional linear accelerators and specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste) are allowed. These units can be used with conformal dose delivery or IMRT. Other specialized accelerators (e.g., the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol.

8.4.4 Simulation/Image Guidance

8.4.5 Patient Positioning

Patients will be positioned in a stable position that allows accurate reproducibility of the target between treatments. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) with any significant probability (i.e., < 5%).

At the time of simulation for patients who will receive SABR to the lung and/or liver, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion

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during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required.

8.4.6 Image Guidance

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images can be obtained with planar kV imaging devices or cone-beam CT equipment. For treatment systems that use kV imaging but also allow EPID imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained.

8.5 Treatment Planning/Target volumes

8.5.1 Image Acquisition

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. CT scan with IV contrast is recommended unless the patient has allergy to contrast or renal insufficiency. Oral GI contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe. Axial acquisitions will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers.

8.5.2 Target Volumes

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). The target will generally be drawn using appropriate windowing based on location of the metastatic lesion(s). 4-dimensional CT image guided GTV delineation to take tumor motion into consideration will be allowed.

For treatment to the lung, the target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (i.e., the GTV and the clinical target volume [CTV] are identical). An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

For treatment to the liver, the following structures are contoured: entire liver, each individual liver gross tumor volume (GTV), each kidney, and the spinal cord. The planning target volume (PTV) is constructed to account for the positional uncertainty of the GTV during treatment. The PTV for each contoured GTV should be at least 5mm larger than the GTV in the axial plane and 1.0 cm larger than the GTV in the craniocaudal plane. Larger margins may be used in cases where greater motion of the hemidiaphragm is observed in simulation despite standard maneuvers to diminish motion.

Treatment to skeletal and paraspinous lesions may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing.

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8.6 Dosimetry

8.6.1 3D-Conformal Planning

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Generally, more beams are used for larger lesion sizes. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor in the case of volumetric imaging) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COMPTV). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter.
Regardless, the point identified as COMPTV must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning typically around 80% but ranging from 60-90%. The prescription dose will be delivered to the margin of the PTV. As such, a “hotspot” will exist within the PTV centrally at the COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

8.6.2 Intensity Modulated Radiation Therapy (IMRT)

IMRT is allowed in this study. The use of IMRT in this study is at the discretion of the treating physician. However, IMRT should be considered only when target coverage, OAR dose limits, or dose spillage are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized (2-3 segments per beam should be adequate), and the area of each segment
should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam’s eye view).

8.6.3 Dose Calculations

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction.

Successful treatment planning will require accomplishment of all of the following criteria:
Maximum dose: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
Prescription isodose: The prescription isodose surface must be ≥ 60% and < 90% of the maximum dose.
Prescription Isodose Surface Coverage**:** The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX > 99%).

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8.6.4 Normal Tissue Dose Constraints

In accordance with the prior Phase I studies [7, 8], certain normal tissue dose constraints must be respected.

The possibility that SABR-induced fibrosis might cause occlusion of large central airways, thus impeding ventilation distal to the occlusion has been well considered. An adjustment to the fractionation scheme may be made if, in the opinion of the treating radiation oncologist, the following conditions apply: (1) the location of a lung lesion is close enough to a large proximal bronchial airway such that occlusion might occur, and (2) compromised ventilation to the segment(s) of lung potentially affected would cause clinically significant adverse consequences.

The same special condition applies in the setting of a patient whose primary lung disease has not been irradiated previously but is present as a PET-positive site of disease, often in proximity to mediastinal structures which is a dose-limiting concern. These patients will be considered by the PI on a case-by-case basis.

The following table lists the specific organ and dose fractionation constraints on normal tissues.

One Fraction

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord and medulla	<0.35 cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	10 Gy	14 Gy	myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Sacral Plexus	<5 cc	14.4 Gy	16 Gy	neuropathy
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	13.6 Gy	16.4 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	17.4 Gy	20.2 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	12.4 Gy	13.3 Gy	stenosis with atelectasis
Rib	<5 cc	28 Gy	33 Gy	Pain or fracture
Skin	<10 cc	25.5 Gy	27.5 Gy	ulceration
Stomach	<5 cc	17.4 Gy	22 Gy	ulceration/fistula
Bile duct			30 Gy	stenosis
Duodenum*	<5 cc <10 cc	11.2 Gy 9 Gy	17 Gy	ulceration
Jejunum/Ileum*	<30 cc	12.5 Gy	22 Gy	enteritis/obstruction
Colon*	<20 cc	18 Gy	29.2 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	39 Gy 22 Gy	44.2 Gy	proctitis/fistula
Ureter			35 Gy	stenosis
Bladder wall	<15 cc	12 Gy	25 Gy	cystitis/fistula
Penile bulb	<3 cc	16 Gy		impotence
Femoral Heads	<10 cc	15 Gy		necrosis
Renal hilum/vascular trunk	15 cc	14 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**

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Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.6 Gy	V-8Gy <37%	Pneumonitis
Liver	700 cc	11 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	9.5 Gy		Basic renal function

***Avoid circumferential irradiation**
**** "point" defined as 0.035cc or less**

Three Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord and medulla	<0.35 cc <1.2 cc	15.9 Gy 13 Gy	22.5 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	18 Gy	22.5 Gy	myelitis
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	24 Gy	neuropathy
Esophagus*	<5 cc	17.7 Gy	25.2 Gy	stenosis/fistula
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	25.8 Gy	30 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	18.9 Gy	23.1 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc <10 cc	15.6 Gy 12.9 Gy	22.2 Gy	ulceration
Jejunum/Ileum*	<30 cc	17.4 Gy	27 Gy	enteritis/obstruction
Colon*	<20 cc	24 Gy	34.5 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	45 Gy 27.5 Gy	49.5 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	10.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	11.4 Gy	V-11Gy<37%	Pneumonitis
Liver	700 cc	17.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15 Gy		Basic renal function

***Avoid circumferential irradiation**
**** "point" defined as 0.035cc or less**

Five Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)

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Spinal Cord and medulla	<0.35 cc <1.2 cc	22 Gy 15.6 Gy	28 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	22 Gy	28 Gy	myelitis
Cauda Equina	<5 cc	30 Gy	31.5 Gy	neuritis
Sacral Plexus	<5 cc	30 Gy	32 Gy	neuropathy
Esophagus*	<5 cc	19.5 Gy	35 Gy	stenosis/fistula
Brachial Plexus	<3 cc	27 Gy	32.5 Gy	neuropathy
Heart/Pericardium	<15 cc	32 Gy	38 Gy	pericarditis
Great vessels	<10 cc	47 Gy	53 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	32 Gy	40 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	21 Gy	33 Gy	stenosis with atelectasis
Rib	<5 cc	45 Gy	57 Gy	Pain or fracture
Skin	<10 cc	36.5 Gy	38.5 Gy	ulceration
Stomach	<5cc	26.5 Gy	35 Gy	ulceration/fistula
Bile duct			41 Gy	stenosis
Duodenum*	<5 cc <10 cc	18.5 Gy 14.5 Gy	26 Gy	ulceration
Jejunum/Ileum*	<30 cc	20 Gy	32 Gy	enteritis/obstruction
Colon*	<20 cc	28.5 Gy	40 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	50 Gy 32.5 Gy	55 Gy	proctitis/fistula
Ureter			45 Gy	stenosis
Bladder wall	<15 cc	20 Gy	38 Gy	cystitis/fistula
Penile Bulb	<3 cc	30 Gy		impotence
Femoral Heads	<10 cc	30 Gy		necrosis
Renal hilum/vascular trunk	15 cc	23 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	12.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy	V-13.5Gy<37%	Pneumonitis
Liver	700 cc	21 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	18 Gy		Basic renal function

***Avoid circumferential irradiation**
**** "point" defined as 0.035cc or less**

Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation. Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

8.7 Intracranial Stereotactic Radiosurgery Dose (SRS) for and Technique

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Patients with up to 10 brain metastases with the maximal size <= 4cm will be treated by SRS in a single fraction. If there are more than 10 intracranial lesions or the size of the largest lesion is >4cm, such patients will be ineligible.

8.7.1 SRS Dose

All supratentorial lesions are treated to the prescribed dose below.

	SRS Dose by lesion diameter		
Diameter (cm)	<= 2.0 cm	>2.0 - 3.0 cm	>3.0 - 4.0 cm
Dose (Gy)	20-24	18	15

For lesions within the brainstem (pons, medulla, and midbrain), the prescription dose will be 10-13 Gy in a single fraction.

Multiple SRS sessions are allowed, as long as all intracranial lesions are treated within 14 days.

8.7.2 SRS Technique, Pre-SRS Image acquisition and target planning with Conformality Index

Protocol SRS will be administered with a linear accelerator (LINAC), Vero ® (BrainLab, Feldkirchen, Germany), CyberKnife ® (Accuray, Sunnyvale, CA) or Gamma Knife® Perfexion (Elektra Instruments, Inc., Atlanta, GA). Fixed-frame stereotactic localization and planning will be used for SRS.

Pre-SRS Image Acquisition: MRI with gadolinium contrast is the recommended imaging method for stereotactic localization. In the case of LINAC, Vero or CyberKnife, MRI with contrast has to be obtained within 14 days of SRS with an acquisition of <= 1.5 mm slice thickness. The stereotactic target is the contrast-enhancing tumor as defined on MRI with contrast.

In patients who cannot tolerate the contrast, other MR sequences may be utilized without the contrast, as long as the target lesion can be clearly demarcated for treatment and follow up.

Conformality Index (CI) is derived from dividing the volume encompassed by the prescription isodose line by the target volume.

$$CI = \text{Rx Isodose Vol} / (\text{Target Vol})$$

The target lesion in the SRS planning MRI will be contoured, and its volume will be calculated. Planning should achieve a conformity index specified below.

Size of Target	Prescription Isodose	Conformality Index
<=1cm	35-100%	≤ 2
1-2cm		≤ 2

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2-3cm		≤ 1.5
3-4cm		≤ 1.25

At least 95% of the target volume must receive the prescription dose; the plan should be adjusted to achieve such coverage by the isodose line between 40-100%. No part of the target should receive less than 90% of the prescription dose.

8.7.3 Normal Tissue Dose Constraints

The following table lists maximum dose limits, in one fraction, to a point or volume within several critical structures of the cranium. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.

Critical Structure and margin	Volume	Volume Max (Gy)	Max Point Dose (Gy)*	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis

* "point" defined as 0.035cc or less

Patients with lesions within or near the above structures and the dose constraints cannot be satisfied, will be deemed ineligible.

8.8 Radiation Therapy Quality Assurance

The radiation oncologist will perform an RT Quality Assurance Review after complete data for the first half of cases (18) enrolled at the University of Texas Southwestern Medical Center. They will perform the final review after complete data for the subsequent 19 cases at the University of Texas Southwestern Medical Center are completed. These cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is an, open-label, two-cohort protocol designed to evaluate the activity of targeted therapy and SABR in *ALK* positive lung adenocarcinoma.

Cohort A will evaluate the combination in *ALK*-inhibitor naïve patients.
Cohort B will evaluate the combination in patients who have received treatment with one prior *ALK* inhibitor.

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Ceritinib will be administered to the patient until disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason including death.

The primary focus of this protocol is identifying response in *ALK*+ lung cancer patients. Patients with IHC positive or FISH probe positive tumors will be treated. Evidence of *ALK* gene rearrangement will also be considered eligible for the trial.

Study Design:
Purpose: of this prospective, single-center, two cohort, non-randomized trial is to evaluate the impact of the combination of ceritinib and stereotactic radiation delivered to patients with *ALK*-rearranged adenocarcinoma. The enhanced efficacy of this combination is to be evaluated specifically with regards to prolongation of clinical benefit of ceritinib. We will also evaluate the safety of this combination of targeted therapy and radiation.

For *ALK*-rearranged patients started on ceritinib and treated with SABR to persisting lesions:
-PFS compared to published historical results with ceritinib alone PFS=7 month for prior crizotinib treated and 10 month for no previous crizotinib therapy (Shaw et al, NEJM 2014).
PFS will be defined as Time to Subsequent Systemic Therapy.

As secondary objectives, we will also report overall survival and time to 2nd and 3rd SABR for each cohort.

	Objective	**Endpoint**
Primary:	Cohort A: Superiority of ceritinib + SABR median PFS compared to historical control of 10 months (expected to be 20 months) Cohort B: Superiority of ceritinib + SABR median PFS compared to historical control of 7 months	Cohort A Median PFS defined as time from initiation of ceritinib until disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason including death. Cohort B: Median PFS defined as time from initiation of ceritinib until disease progression by RECIST 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason including death.
Secondary:	Report Overall survival Report Time to 2nd SABR Report Time to 3rd SABR Report proportion of patients CR/PR/stable disease at 6 and12 months	Overall survival Time from start of systemic therapy to first day of second course of SABR Time from start of therapy to first day of third course of SABR Number of patients with CR/PR/stable disease for 6 and 12 months after initiation
Safety:	Demonstrate safety of ceritinib followed by SABR	Describe toxicity and adverse events (CTCAE v.4) compared to historical controls.

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9.2 Sample Size and Accrual

The results of a Phase I trial of ceritinib in *ALK*-rearranged metastatic adenocarcinoma were reported recently (Shaw et al., 2014). Ceritinib demonstrated activity in patients with an overall response rate of 57% at doses of 400 mg or greater. The PFS reported was 7 months for those with prior crizotinib treatment and 10 months for those who had not received any crizotinib. Toxicities and adverse events were also reported. This study offers contemporary, relevant historical control data for comparison purposes.

The sample size calculation is based on the primary endpoint, progression-free survival, and the assumption that patients are randomized until the end of accrual. The sample size is calculated separately for each cohort.

Cohort A (no prior ALK-inhibitor):

A sample size of 18 patients achieves 80% power to detect the difference between the null hypothesis of median PFS of 10 months and the alternative hypothesis of median PFS of 20 months at two-sided significance level of 0.1. We assume the patient accrual period of 36 months and the follow-up period of 12 months. The assumption that patients are randomized until the end of accrual. The sample size was estimated using SWOG (https://www.swogstat.org/stat/public/one_survival.htm) sample size calculator.

Cohort B (treated with one prior ALK inhibitor):

A sample size of 15 patients achieves 80% power to detect the difference between the null hypothesis of median PFS of 7 months and the alternative hypothesis of median PFS of 14 months at two-sided significance level of 0.1. We assume the patient accrual period of 36 months and the follow-up period of 12 months. The assumption that patients are randomized until the end of accrual. The sample size was estimated using SWOG (https://www.swogstat.org/stat/public/one_survival.htm) sample size calculator.

9.3 Data Analyses Plans

We will use Kaplan-Meier methods to estimate the progression-free survival, time to 2nd and 3rd SABR and overall survival.

Duration of response (defined in 6.1.5) duration will be summarized for patients who responded. Descriptive summary statistics like median, 25% and 75% percentiles will be used.

Toxicities are dichotomized as none versus any, or none and mild versus moderate to severe.

The rates of overall response, toxicity and adverse events as well as their 95% confidence intervals will be estimated using exact binomial method.
We will compare the rates of toxicity and adverse events in this study with those of historical controls by the Fisher's exact test.

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9.3.1 Treatment phase and duration of treatment

Patients eligible for treatment will receive 450 mg daily of ceritinib as part of a 28 day cycle. The first dose of each cycle will be administered after evaluation at the study center. Patients will remain on study and take ceritinib until there is evidence of disease progression by RECIST, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

If there is oligoprogression amenable to SABR, resumption of ceritinib after SABR will be permitted if the treating oncologist feels the patient would benefit.

9.4 Definition of end of the Study

Cohort A will be completed when 20 patients and cohort B will be completed when 17 patients have evidence of disease progression by RECIST not amenable to SABR requiring discontinuation of ceritinib, unacceptable toxicity, withdrawal of consent, or discontinuation of the trial for any other reason.

At the completion or discontinuation of study medication, all patients will be seen within 30 days for an end of therapy evaluation. This will include a safety assessment for AE's SAE's. Any unused medication will be returned.

9.5 Early Termination

Treatment on protocol may be terminated early if the Principal investigator or institution assess that the safety of the enrolled subjects will be compromised by continuation of the trial. The procedure followed will be that of the premature withdrawal patient and any patients on treatment will be seen as soon as possible.

9.6 Data confidentiality

Information about protocol subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this protocol
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled protocol treatment period.

9.7 Statistical methods and data analysis

9.8 Analysis sets

9.8.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all enrolled patients.

9.8.2 Safety Set

The Safety Set includes all patients who received at least one dose of ceritinib medication.

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9.9 Patient demographics/other baseline characteristics
Demographic, disease characteristics and other baseline data will be summarized descriptively for the FAS.

9.10 Treatments (ceritinib treatment, concomitant therapies, compliance)
All analyses from this section will be performed on all patients from the safety set. Duration of ceritinib treatment exposure will be summarized.

9.10.1 Handling of missing values/censoring/discontinuations
All attempts will be made to ensure that the database contains full information for the safety set. No imputation will be applied for missing data.

9.10.2 Safety objectives
The safety objective is to describe toxicities in patients treated with ceritinib.

9.10.2.1 Analysis set and grouping for the analyses
For all safety analyses, the safety set will be used. Toxicities will be dichotomized as none versus any adverse event, or none and mild versus moderate to severe adverse event.

The safety summary tables will include assessments from the on-treatment period, unless otherwise specified.

All safety data collected in the study will be listed regardless of the study period with data collected during the pre-treatment and post-treatment period flagged.

9.10.2.2 Adverse events (AEs)
Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified category, number and percentage of patients with at least one event per category will be summarized.

9.10.2.3 Other safety data
Other safety data (including ECGs, vital signs and weight) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

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10.0 Ethical considerations and administrative procedures

10.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients will only be included on this after providing written IRB/IEC/REB-approved informed consent.
Informed consent must be obtained before conducting any protocol-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in the clinical trial record. The informed consent document will be approved by the IRB.

10.3 Discontinuation of the study

This study will discontinue if terminated by the Institutional Review Board or at the discretion of the Principal Investigator.

10.4 Publication of the study and results

The results of this study will be updated and posted per regulatory requirements, including (but not limited) to databases such as clinicaltrials.gov.

10.4.1 Communication and Publication of Clinical Trial Results

All submitted manuscripts will comply with institutional guidelines and with authorship guidelines of the International Committee of Medical Journal Editors.

10.5 Study documentation, record keeping and retention of documents

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

10.6 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any trial documents. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification.

10.7 Audits and inspections

Source data/documents must be available to inspections by Health Authorities.

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11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

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

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

11.3 Registration Procedures

All subjects must be registered with the Clinical Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Clinical Research Office Study Coordinator or Manager. To register a subject, call 214 648 5874 Monday through Friday, 9:00AM-5:00PM.

11.4 Data Management and Monitoring/Auditing

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity review will be performed at the annual monitoring review. These reviews will be documented by a written audit report, within 2 weeks of audit completion. The findings are reviewed with the research team to review any discrepancies and discuss corrective action. Audit reports and responses are distributed for review to the Deputy Director of the Cancer Center, DSMC Chairman, PI, DOT Leader and Associate Direction of the CRO.

The DOT will review all local serious adverse events and unanticipated problems at monthly DOT research meetings. The discussion of such events is documented in the meeting minutes. Events are reported by the research coordinator to the DSMC per the DSMC plan.

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The UTSW Simmons Cancer Center (SCC) Data and Safety Monitoring Committee (DSMC) is responsible for overall monitoring of data quality and patient safety. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The Quality Assurance activity of the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance based on risk.

The SCC-DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it is the DSMC of record.

Further detail may be found in the SCC-DSMC Plan.

11.5 Adherence to the Protocol

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

11.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

11.5.2 Other Protocol Deviations/Violations

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

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

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

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

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

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

Protocol Violations: Study personnel should report violations within two (2) weeks of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

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11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 Appendices

13.1 Appendix 1: List of prohibited concomitant medications and concomitant medications requiring caution for ceritinib

Table 14-1 Prohibited medications that are strong inducers or inhibitors of CYP3A, or CYP3A substrates with narrow therapeutic index, or sensitive CYP2C substrates with narrow therapeutic index**

CYP2C8 substrates with narrow therapeutic index			
Paclitaxel			
CYP2C9 substrates with narrow therapeutic index			
Warfarin	phenytoin		
CYP3A4/5 substrates with narrow therapeutic index			
astemizole*	diergotamine	pimozide	alfentanil
cisapride*	ergotamine	quinidine*	terfenadine*
cyclosporine	fentanyl	tacrolimus	sirolimus
Strong CYP3A4/5 inhibitors			
Macrolide antibiotics:	**Antivirals:**	**Antifungals:**	**Others:**
clarithromycin	indinavir	itraconazole	conivaptan
telithromycin	lopinavir	ketoconazole	elvitegravir
troleandomycin	nelfinavir	posaconazole	mibefradil
	ritonavir	voriconazole	nefazodone
	saquinavir		
	tipranavir		
Strong CYP3A/5 inducers			
avasimibe	carbamazepine	phenobarbital	Phenytoin
rifabutin	rifampin	St. John's wort	

* Compounds with risk of QT prolongation

For an updated list of CYP2C substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.

**Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

Table 14-2 List of medications to be used with caution

CYP2B6 substrates			
cyclophosphamide	ifosfamide	thiotepa	Bupropion
efavirenz	methadone		
CYP2C8 substrates			
amodiaquine	cerivastatin	repaglinide	Rosiglitazone
torsemide			
CYP2C9 substrates			

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losartan	irbesartan	diclofenac	ibuprofen
piroxicam	tolbutamide	glipizide	acenocoumarol
celecoxib	sulfamethoxazole	tolbutamide	torsemide

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CYP3A4/5 substrates			
dronedarone	capravirine	aripiprazole	casopitant
alprazolam	ritonavir	haloperidol	quinine
diazepam	telaprevir	imatinib	tamoxifen
amlodipine	atorvastatin	nilotinib	tolvaptan
diltiazem	everolimus	methadone	trazodone
nifedipine	clarithromycin	boceprevir	vincristine
nisoldipine	erythromycin	brecanavir	verapamil
nitrendipine	telithromycin		
Moderate CYP3A4/5 inhibitors			
ciprofloxacin	darunavir	grapefruit juice	dronedarone
erythromycin	fosamprenavir	aprepitant	tofisopam
amprenavir	diltiazem	casopitant	
atazanavir	verapamil	cimetidine	
Moderate CYP3A4/5 inducers			
bosentan	efavirenz	etravirine	modafinil
nafcillin	ritonavir	talviraline	tipranavir
Proton pump inhibitors			
esomeprazole	lansoprazole	omeprazole	Pantoprazole
rabeprazole			
This database of CYP 2B6, 2C8, 2C9 and 3A4/5 substrates, 3A4/5 inhibitors and inducers is from the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (www.druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies"			

Table 14-3 List of prohibited enzyme-inducing anti-epileptic drugs

Prohibited enzyme-inducing anti-epileptic drugs			
carbamazepine	ethotoin	felbamate	fosphenytoin
phenobarbital	phenytoin	primidone	topiramate

Table 14-4 List of prohibited QT prolonging drugs

Prohibited medications causing QTc prolongation			
Antiarrhythmic:	**Anticancer:**	**Antibiotic:**	**Antianginal:**
amiodarone	arsenic trioxide	azithromycin	bepridil
disopyramide	vavdetanib	clarithromycin*	**Antipsychotic:**
dofetilide	**Antihistamine:**	erythromycin*	chlorpromazine
flecainide	astemizole*	moxifloxacin	haloperidol*
ibutilide	terfenadine*	sparfloxacin	mesoridazine
procainamide	**Antimalarial:**	**Antinausea:**	pimozide
quinidine*	chloroquine	domperidone	thioridazine
sotalol	halofantrine	droperidol	**Opiate agonist:**
Antilipemic:	**Anti-infective:**	**GI stimulant:**	levomethadyl
probucol	pentamidine	cisapride*	methadone
Antidepressant:			

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citalopram			

Please note: *CYP3A substrate
Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes, http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm

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