LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #5: LCCC1123
DATED 11/18/2014

LCCC 1123: Phase II Study Of Stereotactic Radiosurgery or Other Local Ablation Followed by Erlotinib for Patients with EGFR Mutation Who Have Previously Progressed on an EGFR Tyrosine Kinase Inhibitor (TKI)

AMENDMENT INCORPORATES:

_ _ Editorial, administrative changes
_X_ Therapy changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Section 4.3 (Erlotinib Treatment Dosage and Administration) required erlotinib be held for 3 days prior to SRS in patients who enroll already receiving this agent. Not all participating sites follow this practice, and data are not clear that one approach is best. Therefore, this requirement has been revised to a recommendation. This change is also reflected in sections 6.1 (Time and Events table, specifically the footnotes), section 6.3.2 (Study Assessments) and section 6.7 (Correlative Studies).

In addition, the UNCCN Study Coordinator has been has changed to UNCCN Project Manager throughout the protocol.

Section 6.9 (Assessment of Efficacy): clarified that local ablative therapy refers to SRS or other local ablative therapy such as surgery

THE ATTACHED VERSION DATED 11/18/2014 INCORPORATES THE ABOVE REVISIONS

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AMENDMENT RATIONALE AND SUMMARY:

The driver for this amendment was clarification of conflicting guidance on the dose and schedule of Stereotactic Radiosurgery (section 4.2) per organ. Guidance now matches the corresponding dosing table for each organ. Specifically:

- Section 4.2.1d (Brain) specified 3 **and** up to 5 fractions per day; now indicates that treatment to be delivered per institutional preference (i.e. on consecutive days versus several per week; one fraction per day)
- Section 4.2.2 (Chest and Lung) specified in sections 4.2.2b and 4.2.2f that patients could have 3-5 **and** 3-10 treatments/fractions; the reference to 3-5 has been removed
- Section 4.2.3 (abdomen) was incomplete. This has been removed as these lesions are rare
- Section 4.2.4 (liver) section 4.2.4f; clarified that 3 to 5 treatments/fractions will be given on consecutive weekdays or every other day
- Section 4.2.5 (spine/soft tissue): deleted reference to dosing schedule in section 4.2.5b as it conflicted with section 4.2.5f; revised dosing schedule in 4.2.5 to indicate dose to be delivered per institutional preference ((i.e. on consecutive days versus several per week; one fraction per day, 1 to 5 fractions)

In addition, the following minor clarifications were made:

- Removed David Morris as Co-Investigator as he is no longer at UNC
- Inclusion criteria Section 3.1.5; clarified that progressive disease is assessed via RECIST1.1
- Section 4.3; clarified that 3 day washout means 3 full days without erlotinib
- Section 6.1 Time and events table: added footnotes to clarify tumor evaluations at progression and follow-up; added note that post SRS visit can occur on last day of SRS; clarified windows allowed around study visits
- Section 6.9 (assessment of efficacy); refined definition of patients evaluable for analysis of efficacy

THE ATTACHED VERSION DATED 6/19/2014 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #3: LCCC 1123
DATED 08/15/2012

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes
_X Scientific changes (IRB approval)
__ _ Therapy changes (IRB approval)
__ Eligibility Changes (IRB approval)

This protocol has been amended to allow multicenter sites participating on this trial to utilize their institutional brand of radiosurgery machine.

Throughout protocol, and particularly in section 4.2:
Section 4.2: We have edited the study to define standard of care (SOC) parameters for stereotactic radiosurgery that are not specific to the CyberKnife® brand.

Rationale: The SOC radiosurgery incorporated in this multicenter protocol was referred to and specific for CyberKnife®. However, the intent of this protocol is not to dictate which SOC radiosurgery is used, as there are many brands of stereotactic radiosurgery. No core content has been modified. The new parameters will not affect in any way how stereotactic radiosurgery is done for UNC patients—it remains SOC. Similarly, it defines the SOC in such a way that parallel procedures will take part at our partner institutions so that their patients will also be treated per SOC.

Minor typographical errors have been corrected throughout protocol

Added Co-Investigators as follows: Julian Rosenman, MD; Timothy Zagar, MD

ATTACH TO THE FRONT OF EVERY PROTOCOL

PROTOCOL AMENDMENT #2: LCCC 1123

LCCC 1123:

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes
_ X Scientific changes (IRB approval)
__ _ Therapy changes (IRB approval)
__ Eligibility Changes (IRB approval)

Section 1.5: Correlative Studies: Details on VeriStrat® assay revised to:

- Reflect updated references further confirming the validation of this assay
- Removed table 5 with analysis from NCIC BR.21 registrational trial indicating predictive ability of VeriStrat when data adjusted for EGFR mutation status
- Removed reference to full NMR peaks from the MALDI-TOF as VeriStrat does not use NMR (this reference to NMR was also removed from Exploratory Objectives

Section 6.7

- This section has been revised to accommodate blinding. Since there are 4 time points for which samples will be taken, the analysis team from Biodesix, Inc. requested these blood samples be blinded.

Section 7.3.3

- Removed Fax # and mailing address to FDA

Section 9.4

- Revised to reflect recent changes in LCCC protocol template

PROTOCOL AMENDMENT #1: LCCC 1123

LCCC 1123:

AMENDMENT INCORPORATES:

__x_ Editorial, administrative changes
_ _ Scientific changes (IRB approval)
__ _ Therapy changes (IRB approval)
__ Eligibility Changes (IRB approval)
___ Other

Throughout study: Typos corrected

Sections 4.3 and 5.1.2 : Manufacturer of erlotinib (Astellas Pharma) has agreed to provide drug free of charge to patients. Sections 4.3 and 5.1.2 were changed to reflect this.

Sections 7.3 and 7.4: These were slightly revised to reflect updated safety reporting language for trials conducted under an IND.

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Funding Source: Astellas Pharma US

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Signature Page

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

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

Version Date: November 18, 2014

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a single arm phase II trial of 40 patients evaluating a novel treatment strategy for patients with epidermal growth factor receptor (EGFR)-mutant non small cell lung cancer (NSCLC). Eligible patients will have just progressed on a EGFR-tyrosine kinase inhibitor (TKI). In the current trial, all sites of progressive disease will be treated with local ablation (primarily stereotactic radiosurgery) followed by the EGFR-TKI erlotinib until disease progression. We hypothesize that this treatment strategy will lead to a progression free survival of at least 3 months.

1.2 EGFR-mutated NSCLC

75% of NSCLC patients present with metastatic disease, with an expected median overall survival (OS) of 10-12 months. Lung cancer progression is multifactorial. Among the influences are cell surface receptors that control intracellular signal transduction pathways. A subset of NSCLC patients harbors an EGFR mutation that particularly drives their cancer, rendering them susceptible to the effects of small molecular EGFR-TKIs such as gefitinib and erlotinib. Almost all patients with the mutation have adenocarcinoma histology. Presence of this mutation is inversely correlated with history of smoking. It is present in 6% of patients with adenocarcinoma who are current smokers, 15% in former smokers, and 52% of never smokers[1]. Treatment of mutated disease with these EGFR-TKIs results in a median PFS (13 months) that exceeds the median OS for non-mutated patients[2]. Beyond the increased survival, toxicity on EGFR-TKIs is very mild compared to cytotoxic chemotherapy, with an acneiform rash and diarrhea being the most common side effects associated with their use.

1.3 Erlotinib

The only FDA approved EGFR-TKI in the United States is erlotinib (Tarceva®). This agent is approved for maintenance treatment of locally advanced or metastatic NSCLC that has not progressed after 4 cycles of platinum-based first-line chemotherapy. It is also approved for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Several studies have compared chemotherapy to EGFR-TKIs in a variety of contexts within NSCLC. Most relevant to the population to be studied here, the OPTIMAL[3] study compared carboplatin plus gemcitabine to erlotinib for first line therapy of metastatic EGFR-mutant NSCLC. PFS was 13.1 months after erlotinib therapy, as compared to 4.6 months after carboplatin plus gemcitabine (hazard ratio (HR)=0.16, 95% confidence interval (CI) 0.10 to 0.26; $p<0.0001$) .

While these impressive results clearly represent an advance in the treatment of NSCLC, all patients inevitably develop resistance and experience disease

progression within 8-14 months of initiating therapy [4-7] and thereafter require second line therapy.

The standard therapy for patients with EGFR mutation who progress on erlotinib is cytotoxic chemotherapy. While cytototoxic chemotherapy is active against EGFR mutated NSCLC, it is less active than erlotinib. For example, patients randomized to the chemotherapy arm of OPTIMAL experienced a 4.6 month PFS in their first line of treatment. In addition to being less active, chemotherapy is more toxic than erlotinib, requires intravenous infusion, and ultimately also lasts only a finite duration.

1.4 Rationale for Incorporation of Local Ablative Therapy

Progression of cancer while on erlotinib may reflect the emergence of a mutant clone. Whether through positive-selection of a resistant clone that was present before starting therapy or from the evolution of such a clone during therapy, it is clear that some of the cancer cells will remain sensitive to erlotinib while others are resistant. This molecular heterogeneity explains the frequently clinically observed mixed response at the time of progression in patients with EGFR mutation on erlotinib. In this situation, many sites of disease remain well controlled with erlotinib while one or a small number of sites progress. If such sites could be eliminated, systemic sensitivity to erlotinib could theoretically be restored. Erlotinib could then be used for systemic control of remaining sites of disease.

Any modality of local control, such as surgery, radiation, or radiofrequency ablation could theoretically be used to eliminate resistant clones. The following section explains the rationale for preferential use of radiation. However, the anatomy of certain sites will be particularly amenable to alternative modalities of local control and the study will allow this.

1.4.1 Radiation for patients with EGFR mutation

EGFR mutant cells are 500-1,000 fold more sensitive to radiation than wild-type cells, a phenomenon that extends to T790M mutant cells (see Figure 1).[8,9] In EGFR wild-type cells exposed to radiation, EGFR rapidly translocates to the nucleus where it binds DNA-PK, a key component of non-homologous end-joining repair. In L858R or ΔE746-E750 cells, this mechanism of radioresistance is defective. EGFR mutant cells do not halt DNA synthesis or progression to mitosis in response to radiation.

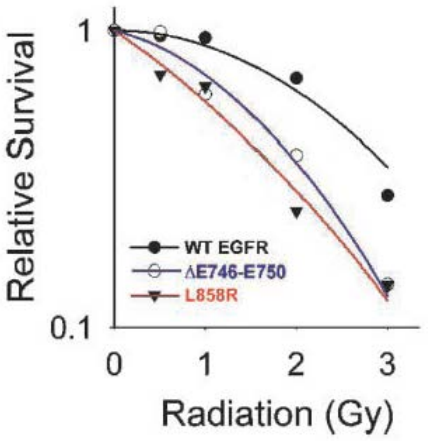


Figure 1

These in-vitro findings are supported by human clinical data. Investigators at the Dana Farber Cancer Institute reviewed their outcomes after thoracic radiation between EGFR mutant and wild-type tumors in a retrospective cohort of patients with locally advanced NSCLC[10]. The two-year locoregional relapse rate was 45.5% in EGFR wild-type patients and 19.1% in patients with EGFR mutation. These findings suggest that radiation may be a particularly effective modality for the treatment of EGFR mutant cancers (see Figure 2).

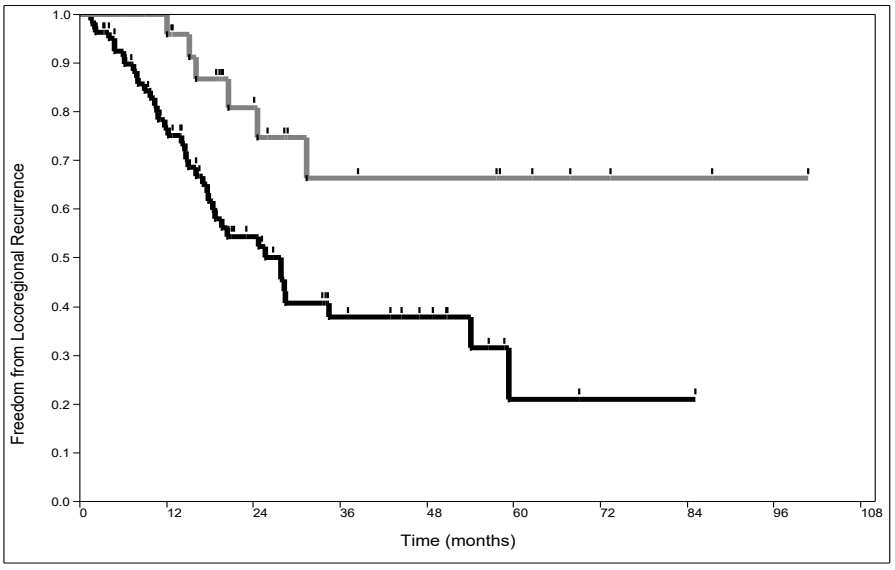


Figure 2 (Grey curve EGFR mutant, Black curve EGFR Wild-Type)

1.4.2 Stereotactic Radiosurgery (SRS)

A number of studies have investigated stereotactic radiosurgery (SRS) for the treatment of cancer. SRS is a method for delivering focused high dose

radiotherapy to a tumor while attempting to spare surrounding normal tissues. It is extremely effective at treating small lesions and with appropriate patient selection, has low toxicity. It can be administered via several different modalities, including linear accelerator based (e.g. Varian's Novalis, Accuray's CyberKnife) which can treat both central nervous system and extracranial disease, as well as the GammaKnife which treats intracranial disease exclusively. Much of the focus of research of SRS in lung cancer has been on cure of small lesions in patients who are not candidates for surgery. However, multiple studies have investigated its use in metastatic disease.

Investigators at the University of Rochester Medical Center treated 49 patients with a total of 125 metastatic lesions and achieved a crude local control rate of 94%[11]. Of note, 8 of these patients had lung cancer; there was a tail to the survival curves for both breast cancer and lung cancer (see Figure 3).

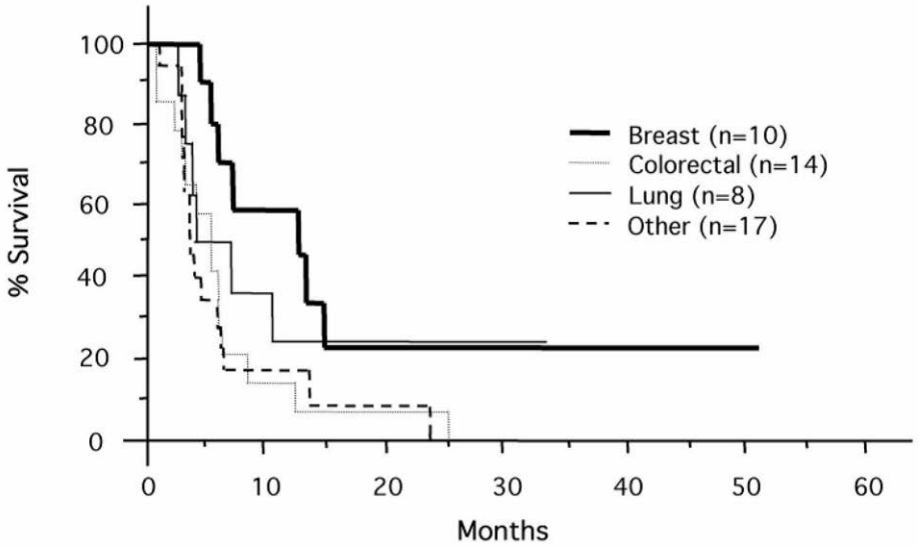


Figure 3

Another study evaluated only patients with metastatic NSCLC, with only 1 or 2 sites of oligometastatic disease[12]. The long term survival rate of 22% in this study was comparable to older studies utilizing primary surgical resection plus metastectomy of isolated adrenal or brain metastases from NSCLC (see Figure 4).

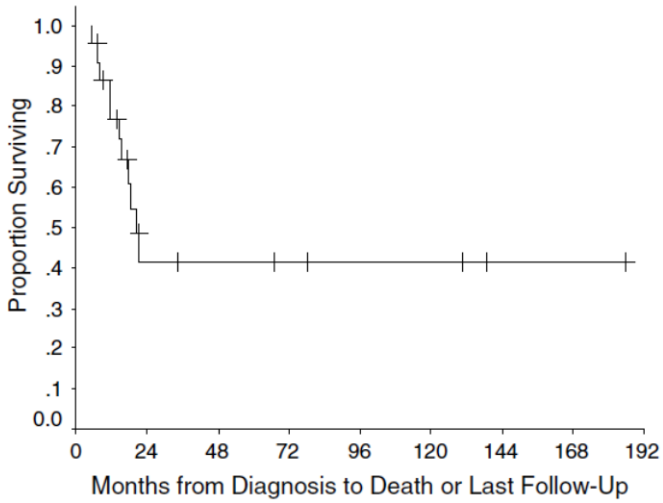


Figure 4

A larger series treated 121 patients with ≤ 5 detectable metastases[13]. As shown in the Figure 5 below, 2 year overall and progression-free survival was 50% and 26% and at four years they were 28% and 20%.

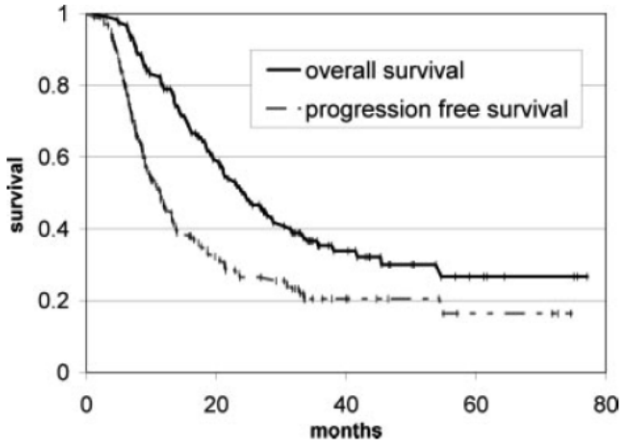


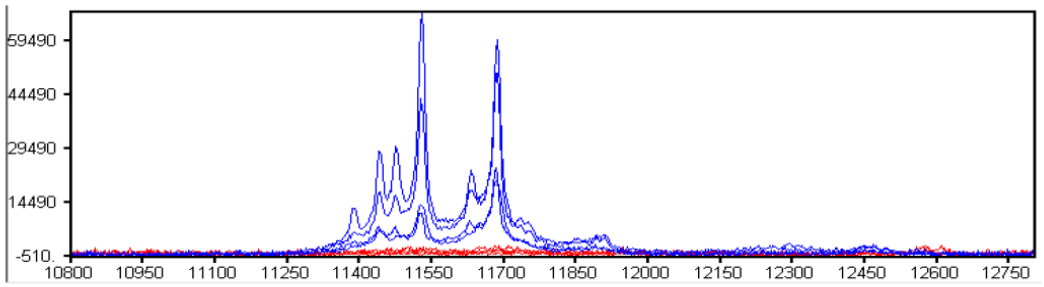
Figure 5

Sufficient data exists on the appropriate use of SRS in body-specific sites that the American Association of Physicists in Medicine (AAPM) has issued guidelines for its use[14].

1.5 Correlative Studies

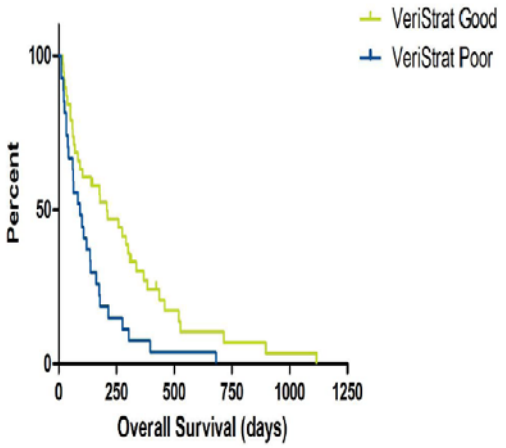
VeriStrat® is a commercially available serum proteomic test that identifies second and third line NSCLC patients who are likely to have a good or poor outcome (as measured by OS) following erlotinib therapy. Serum is analyzed

using Matrix Assisted Laser-Desportion Ionization Time of flight Mass Spectrometry (MALDI-TOF). Eight peaks are analyzed to create a result of "good" or "poor."



VeriStrat® was initially developed on a training set of 139 patients who were treated with gefitinib and validated on two additional cohorts of patients receiving EGFR TKIs[15]. While the test was able to predict outcomes in patients treated with an EGFR-TKI, it did not distinguish results from patients treated with chemotherapy.

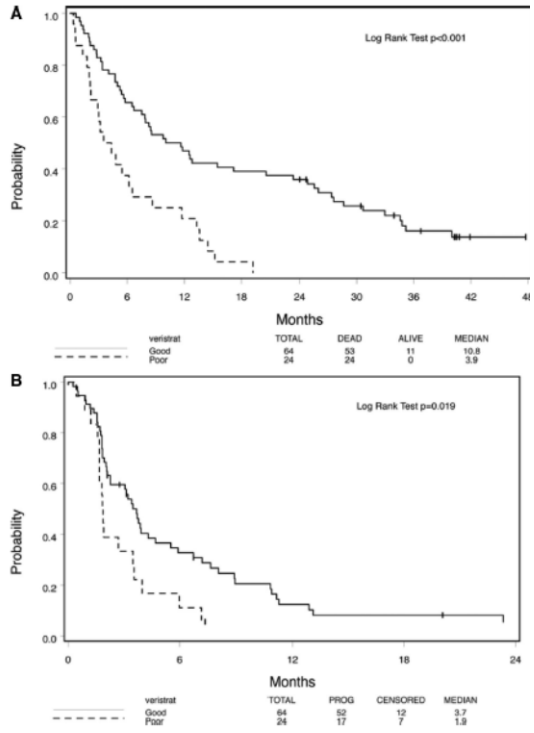
The plot below shows the overall survival by VeriStrat group of one of the original VeriStrat validation cohorts, patients treated in second-line with gefitinib. These data (on file at Biodesix), updated from those published originally[15], yield a hazard ratio between VeriStrat groups of 0.45 (95% confidence interval: 0.25-0.80), log-rank p=0.006.



Interestingly, sera were available from 29 patients who progressed on gefitinib in this series. 22 of these patients were VeriStrat® good at the initiation of the study and 11 (50%) of these converted to VeriStrat® poor at the time of withdrawal from study therapy[16].

Similar results were found in an analysis of ECOG 3503, a single-arm phase II study of erlotinib for first line therapy of NSCLC[17]. Of 137 enrolled patients, analyzable samples were available on 102. VeriStrat® identified 73% of these as

having a good signature and 27% as having a poor signature. As shown below, both OS and PFS were different for patients with good and poor signatures.



A retrospective analysis of the 441 available pretreatment plasma samples from the NCIC BR.21 registrational study of erlotinib versus placebo in second- and third-line advanced NSCLC patients confirmed that patients classified as VeriStrat Good have significantly better outcomes than those classified as VeriStrat Poor. Multivariate analysis showed that VeriStrat remains a significant predictor of OS when adjusted for other patient characteristics, including EGFR mutation status. In addition to showing in the placebo arm that VeriStrat has a clear prognostic component, this study demonstrated that VeriStrat was predictive of response to erlotinib, with all but one of the 19 responders being classified as VeriStrat Good[18].

A study has been undertaken to investigate changes in patient VeriStrat classification during the course of gefitinib therapy.[16] It was found that, although VeriStrat classifications remained generally stable during the course of treatment, in approximately 30% of the patients classified as VeriStrat Good at baseline, the classification changed to VeriStrat Poor near progression. Progression in these patients was found to be associated with the development of new lesions. Changes of VeriStrat classification from VeriStrat Poor to VeriStrat Good during the course of treatment were observed, but were rare.[16]

There are several advantages to the use of this assay for biocorrelative studies. First, the test is non-invasive so there would be minimal risk or discomfort to the

patient and no harm to study accrual secondary to reluctance to undergo a biopsy. Second, the test is commercially available and standardized.

Serum will be collected for testing with the VeriStrat® MALDI-TOF assay. Several exploratory objectives will be evaluated. We will evaluate if VeriStrat® at the time of initial progression on TKI predicts for longer PFS or OS. We will evaluate if VeriStrat® following completion of SRS predicts for longer PFS or OS with re-initiation of erlotinib. We will evaluate whether "poor" VeriStrat® signatures ever turn to "good" signatures following SRS. We will evaluate PFS and OS of patients whose signature changes from "poor" to "good." . We will explore response rates and PFS on subsequent treatments (see section 6.5).

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To estimate PFS after locally ablative therapy and erlotinib in EGFR-mutant NSCLC patients who progressed on prior EGFR-TKI therapy

2.2 Secondary Objectives

2.2.1 To evaluate local control of sites previously progressive on erlotinib following SRS followed by erlotinib

2.2.2 To estimate OS after locally ablative therapy and erlotinib in EGFR-mutant NSCLC patients who progressed on prior EGFR-TKI therapy

2.2.3 To characterize the toxicity of SRS

2.2.4 To characterize the toxicity of erlotinib when preceded by SRS

2.3 Exploratory Objectives

2.3.1 To explore if VeriStrat® results at the time of initial progression on EGFR-TKI are associated with longer PFS or OS with the study therapy of SRS followed by erlotinib

2.3.2 To explore if VeriStrat® results following completion of SRS are associated with longer PFS or OS after re-initiation of erlotinib

2.3.3 To explore whether "poor" VeriStrat® signatures ever turn to "good" signatures with the study therapy, and to explore PFS and OS of patients whose signature changes

2.4 Endpoints

2.4.1 Primary

PFS will be measured from the time of initiation of SRS until disease progression or death from any cause

2.4.2 Secondary

- OS will be measured from the time of initiation of SRS until death from any cause
- Local control rate of sites ablated by SRS will be measured both overall and by lesion
- Toxicity of SRS will be measured by NCI CTCAE version 4 following completion of SRS, but prior to erlotinib re-initiation.
- Toxicity of erlotinib will be graded using NCI CTCAE version 4.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subject must meet all of the inclusion criteria listed below to participate:

3.1.1 Written informed consent has been obtained.

3.1.2 ≥18 years of age

3.1.3 Histologically or cytologically confirmed stage IV EGFR-mutant NSCLC or, in the absence of availability of EGFR testing (for example, inadequate tissue), clinical response overwhelmingly consistent with EGFR mutation (PR plus at least 6 months free of progressive disease as a consequence of EGFR-TKI therapy).

3.1.4 History of previous response to EGFR-TKI, defined as either a PR by RECIST1.1 criteria, or at least six months without progressive disease as a result of EGFR-TKI therapy

3.1.5 Progressive disease as measured via RECIST1.1 following EGFR-TKI therapy (with ≤5 sites of disease amenable to SRS or other locally-ablative treatment)

3.1.6 Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

3.1.7 Adequate organ and marrow function as defined below:

- Absolute neutrophil count [ANC] ≥ 1,500 cells/μL
- Hemoglobin ≥ 10 g/dL
- Platelets ≥ 100,000/μL
- Serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/min
- Total bilirubin ≤ 3.0 x upper limit of normal [ULN]

- Alanine aminotransferase [ALT] ≤ 2.5 x ULN
- Aspartate aminotransferase [AST] ≤ 2.5 x ULN

3.1.8 Female patients must have a negative urine or serum pregnancy test at screening (pregnancy test not required for patients with bilateral oophorectomy and/or hysterectomy or for those patients who are > 1 year postmenopausal).

3.1.9 All patients of reproductive potential must agree to use adequate contraception

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria listed below at baseline will be excluded from study participation:

3.2.1 Any unresolved chronic toxicities > grade 2, measured by CTCAE v4.

3.2.2 Treatment with any FDA approved or experimental cancer treatment following progression on EGFR-TKI (e.g., radiation or chemotherapy; supportive regimens such as denosumab or zoledronic acid will not result in exclusion)

3.2.3 Any history of previous ≥ grade 3 toxicity attributable to erlotinib (except dermatological toxicity)

3.2.4 Pregnant or lactating female

3.2.5 Any previous radiation to sites of planned SRS. A patient may be deemed eligible in this case if a non-radiation mode of local ablation such as surgical resection is deemed safe and feasible by the PI.

3.2.6 History of another malignancy; **exception**: Subjects who have been disease-free for 3 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible.

3.2.7 Concomitant anticancer therapy, immunotherapy, or radiation therapy (no radiation within prior 4 weeks)

3.2.8 Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, or cardiac disease)

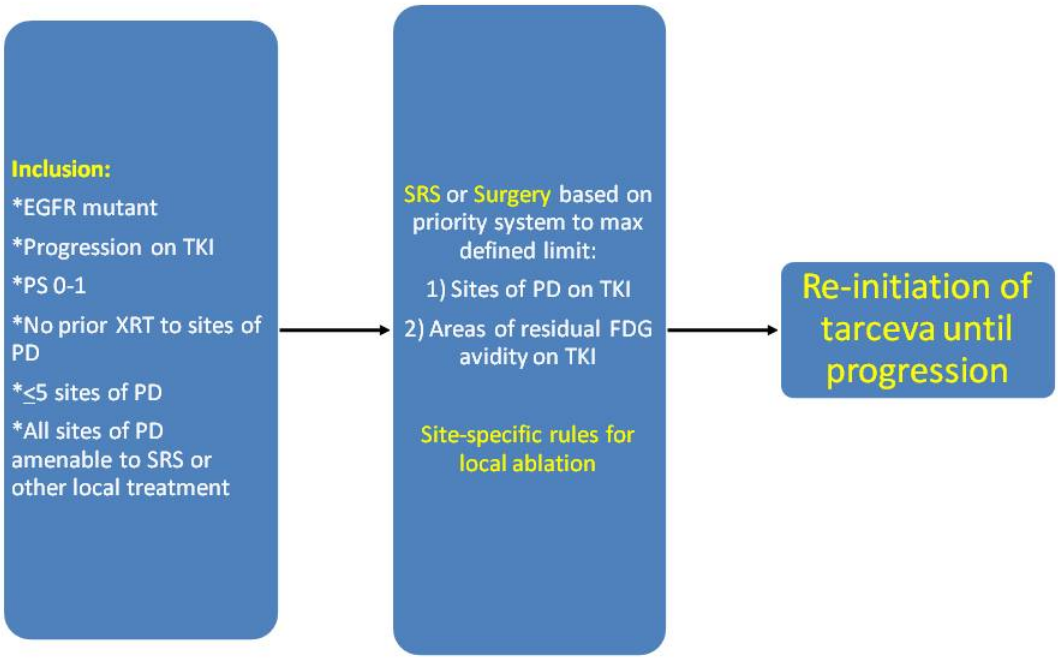
3.2.9 Known hypersensitivity reaction or idiosyncrasy to erlotinib

3.2.10 Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol

3.2.11 Any other concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol

4.0 TREATMENT PLAN

4.1 Schema



The study will be a single arm non-randomized phase II study of forty patients. We anticipate completing accrual over a 2 year period.

4.2 Steroeotactic Radiosurgery

All sites of progressive disease will be treated with SRS, unless an alternative locally ablative option is chosen. A maximum of five sites will be treated. If less than five sites have progressed on erlotinib, additional sites up to a total of 5 sites may be treated, at the discretion of the treating radiation oncologist. Guidelines for SRS will be defined by body site, consistent with standard of care radiation, as reviewed below.

4.2.1 Radiosurgery Therapy: Brain

4.2.1a Equipment

Modality: Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including isocentric conical collimators, mini-multi-leaf (5 mm or less) technology or linear accelerators mounted on robotic arms.

4.2.1b Treatment technique

An immobilization/patient localization system is mandatory for this study. Multiple isocenter and non-isocentric techniques are permitted.

4.2.1c Treatment volumes

The goal of treatment planning is to deliver a conformal dose of radiation to the contrast enhancing target volume based on MR or CT images. Treatment volumes will be determined based on correlation of diagnostic imaging with a treatment planning CT scan performed at 1.00 to 1.25mm slice thickness. Minimal margins are allowed of up to 3 mm will be used. Typically, no margin is used except in the setting of issues of indistinct borders. The relevant target volumes and critical structures for treatment planning will be contoured by the participating radiation oncologist and/or neurosurgeon. Both radiation oncologist and neurosurgeon need to review the target volumes. When a patient is able to undergo a MRI, MRI will be used with formal image registration. The preferred image is a T1 image post-gadolinium at a minimum of 3 mm between image slices. The MRI does not need to be performed in the treatment planning position.

The GTV is defined as the gadolinium-enhanced T1 image abnormality. In the setting of treating post-surgically, the tumor bed (resection cavity) as defined on the T1 gadolinium enhanced image will be treated. This can be termed GTV or CTV. No PTV will be defined unless there is evidenced of registration error. The use of a PTV will be at the discretion of the treating physicians but should not be greater than a 3 mm 3D expansion.

4.2.1d Treatment schedule / time and dose considerations

Radiosurgery treatments will be delivered per institutional preference (on consecutive weekdays versus several per week;one fraction per day).

Time and dose considerations:

- *Prescription isodose*: The dose will be calculated to the 50-100% isodose curve as normalized to the maximum dose. Dose is specified in Gray (Gy) to muscle.
- C*overage*: The target lesion should be covered at least 95% by the prescription isodose curve; small volume lesions (those treated with a single 5 mm collimator and have a high conformity (>1.8) index) may be covered with less than a 95% but not less than 90%
- C*onformity of dose*: Conformity indices PIV*TIV/TV^2 should be within 1.00 – 1.80; small volume lesions (those treated with a single 5 mm collimator and have a high conformity (>1.8) index) may be treated with a conformity index < 2.0
- *Total dose*: The total dose is to the prescription isodose

- *Normal tissue dose limitations*: The dose to the optic chiasm and nerves will be < 8 Gy if a single fraction, < 15 Gy in 3 fractions, < 25 Gy in 5 fractions; if there has been prior radiation acceptable tolerance limits are < 6 Gy single fraction, < 12 Gy in 3 fractions, < 20 Gy in 5 fractions. Brainstem will be < 15 Gy per fraction or total cumulative dose of < 20 Gy unless tumor is intrinsic to the brainstem. Volume of brain receiving >12Gy should be limited to <10cc in a single fraction treatment. Volume of brain for fractionated treatment will not have a limit
- *Dose schedule*: Patients will receive one treatment daily, delivered per institutional preference (on consecutive days versus several per week; one fraction per day)

Max diameter of single tumor or volume	**Fraction #**	**Total Dose (isodose prescription, NOT max dose)**
<1 cm (<0.5cc)	1	20 Gy
1-2 cm (0.5 cc-4.2cc)	1	18-20 Gy
2-3 cm (4.2cc-14.1cc)	1 3	18 Gy 18-21 Gy
3-4.5 cm(14.1 cc-47.7 cc)	1 3	15 Gy 18-21 Gy
>4.5 cm (>47.7cc)*	5	25 Gy
*In general tumors greater than 6 cm or 133 cc should not be treated with stereotactic radiosurgery		

RTOG SRS QA Guidelines will be followed and AAPM Report 54 Guidelines will be followed

Please note: based on anatomic location, edema/mass effect, and patient's extracranial disease status doses can be reduced by 10% or converted to fractionated treatment. Normal tissue tolerance limits that are specified should be respected unless there are special circumstances.

Anatomic locations where dose reduction or fractionation can be considered are posterior fossa, deep and central (thalamic, insular, brainstem) or motor strip (or adjacent to motor strip). Dose reductions are allowed but not required. This will require clinical judgment.

Although we rarely treat more than 4 intracranial lesions, when doing so dose is 16 Gy to the lesions.

4.2.2 Radiosurgery Therapy: Chest and Lung

4.2.2a Equipment

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 10 MV but not > 15 MV will be allowed only for a limited number (≤ 2) beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter.

4.2.2b Treatment technique

Inverse treatment planning will be employed using isocentric and/or non-isocentric beam arrangements..

4.2.2c Treatment volumes

The goal of treatment planning is to deliver a conformal dose of radiation to the contrast enhancing target volume based CT images. Treatment volumes will be determined based on correlation of diagnostic imaging with a treatment planning CT scan performed at 1.00 to 1.50 mm slice thickness. Minimal margins of up to 3-10 mm will be used. The relevant target volumes and critical structures for treatment planning will be contoured by the participating radiation oncologist and/or thoracic surgeon. The preferred image for target contouring is a CT image post-contrast at a minimum of 1.5 mm between image slices with the image obtained at the normal end expiratory cycle. When a patient is unable to maintain a breath hold for the entire scan (which is an expected common occurrence) the breath hold at end expiration should be performed through the region where the tumor is located or the therapists can determine the optimal breath hold technique for compliance with the planning scan. If a breath hold technique cannot be performed a 4D-CT scan should be obtained.

Note: FOV on the “big bore” CT should be limited to 60 cm to avoid intentional artifact that may impact dose algorithm.

4.2.2d Treatment simulation

- The simulation procedure will involve obtaining the CT dataset in the treatment position and at normal end-expiratory breath hold throughout the region of interest. If this cannot be accomplished the optimal breath hold technique can be determined by the therapist.
- All patients will be simulated in the supine position, head at the superior portion of the treatment/simulation table.
- In general, the patient’s head will be in the neutral position or in a position that maintains a comfortable airway
- The CT dataset for treatment planning will be obtained at 1.00 mm to 1.5 mm slice thickness and will be a non-contrast study
- The patient’s head and body should remain in the PDP safety zone.

- A contrasted CT scan will be obtained in the treatment position after the non-contrast study has been obtained in a similar fashion as the non-contrasted study.

4.2.2e Treatment immobilization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, 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%).

4.2.2f Treatment schedule / time and dose considerations

Time and dose considerations:

- *Prescription isodose*: The dose will be calculated to the 60-100% isodose curve as normalized to the maximum dose. In general, the 60-85% isodose curve is strived for target coverage
- *Coverage*: The target lesion should be covered at least 95% by the prescription isodose curve and 99% should be covered by 90% of the prescription isodose curve
- *Conformity of dose*: Conformity indices $PIV*TIV/TV^2$ should be within 1.00 – 1.80 at 2 cm from the PTV, the dose should be no greater than 30 Gy. The ratio of 50% isodose volume to the prescription Isodose volume should be no greater than 3.9
- *Total dose*: The total dose to the prescription isodose
- *Normal tissue dose limitation:* The dose to the whole lung (bilateral) will be a V20 of < 15% the dose to the spinal cord < 18 Gy with no fraction greater than 6 Gy (to < 0.1 cc) esophagus < 27 with no fraction greater than 9 Gy heart/ proximal bronchus/trachea/ great vessels < 30 Gy with no fraction greater than 10 Gy (to < 3 cc) brachial plexus < 24 Gy with no fraction greater than 8 Gy (to < 3 cc)
- *Dose schedule*: Radiosurgery will be delivered using three to ten treatments delivered using an every other day to twice weekly regimen for fraction schemes less than or equal to 5 treatments and a daily treatment regimen (exception for weekends) for fractionation schemes greater than 5 treatments .

Max diameter of single tumor	Fraction #	Total Dose
<4 cm	3 4	54-60 Gy 48 Gy (preferred)
4-6.5 cm	4	48 Gy
Tumors located within 2 cm of the mainstem bronchi, adjacent to chest wall, or prior radiation	4 10 3 4	48 Gy 50 Gy 24-30 Gy (prior RT in central location) 48 Gy (can be considered for near chest wall, no limit on chest wall except not higher than prescription dose)
Multiple Lesions	4 10	48 Gy 50 Gy

QA Guidelines will be followed and AAPM Task Force Group 101 (AAPM Report 101). Guidelines will be followed and the ASTRO/ACR Practice Guidelines in regard to treatment (not personnel) will be followed

NB: In all circumstances, normal tissue tolerances need to be respected and dose reductions will be acceptable to meet those criteria

In general margin for PTV will be determined by the ability to track the tumors as orientation of the tumors and the directions in which they move can vary. The minimum margin will be 3 mm isotropically. In most circumstances, the margin will be 5 mm isotropically when tracking of 3 fiducials is feasible; the placement of fiducials is preferable, but not mandatory. In circumstances in which fiducial marker tracking is not able to compensate for rotation (i.e., less than 3 fiducials), margins may be increased up to 10 mm in all dimensions or anisotropically at the disretion of the radiation oncologist. Evaluation under fluoroscopy to try to assess movement would be reasonable to assist in determining margins.

If fiducials cannot be placed, internal target volume (ITV) can be used with daily image guidance

4.2.4 Radiosurgery Therapy: Liver

4.2.4a Equipment

Only photon (x-ray) beams produced by linear accelerators with photon energies of 4-10 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Photon beam energies > 10 MV but not > 15 MV will be allowed only for a limited number (≤ 2) beams that

must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter.

4.2.4b Treatment technique

Inverse treatment planning will be employed using isocentric and/or non-isocentric beam arrangements.

4.2.4c Treatment volumes

The goal of treatment planning is to deliver a conformal dose of radiation to the contrast enhancing target volume based on MR or CT images. Treatment volumes will be determined based on correlation of diagnostic imaging with a treatment planning CT scan performed at 1.00 to 1.50 mm slice thickness. Minimal margins of up to 3 mm beyond the GTV will be used for microscopic tumor spread (CTV) respecting normal anatomic boundaries. The preferred margin is 3-5 mm in all dimensions. PTV should include an additional margin of 1.5-5 mm depending on location of the fiducial markers, image registration quality, tumor deformation, and the patient's respiratory pattern. The relevant target volumes and critical structures for treatment planning will be contoured by the participating radiation oncologist and/or surgeon. Both radiation oncologist and surgeon need to review the target volumes. The preferred image for target contouring is a CT image post-contrast at a minimum of 1.5 mm between image slices with the image obtained at the normal breathing cycle.

4.2.4d Treatment simulation

- The simulation procedure will involve obtaining the CT dataset in the treatment position and during the normal breathing treatment through the region of interest.
- All patients will be simulated in the supine position, head at the superior portion of the treatment/simulation table.
- In general, the patient's head will be in the neutral position or in a position that maintains a comfortable airway
- The CT dataset for treatment planning will be obtained at 1.00 mm to 1.5 mm slice thickness and will be a non-contrast study
- The patient's head and body should remain in the PDP safety zone.
- A contrasted CT scan will be obtained in the treatment position after the non-contrast study has been obtained in a similar fashion as the non-contrasted study.
- CT simulation will be obtained with end expiratory breath hold through the lesion and fiducial markers (if placed).

4.2.4e Treatment immobilization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, 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%).

4.2.4f Treatment schedule / time and dose considerations

Time and dose considerations:

- *Prescription isodose*: The dose will be calculated to the 60-100% isodose curve as normalized to the maximum dose. In general, the 60-80% isodose curve is strived for target coverage
- *Coverage*: The target lesion should be covered at least 95% by the prescription isodose curve and 99% should be covered by 90% of the prescription isodose curve
- *Conformity of dose*: Conformity indices PIV*TIV/TV^2 should be within 1.00 - 2.00
- *Total dose*: the total dose to the prescription isodose
- *Normal tissue dose limitations*: The dose to the whole lung (bilateral) will be a V20 of < 15% esophagus < 30 Gy with no fraction greater than 10 Gy (to 3cc or greater) stomach < 30 Gy (to 3 cc or greater) heart < 30 Gy with no fraction greater than 10 Gy. The maximum voxel dose to the spinal cord should not exceed 12 Gy in a single fraction and should be < 15 Gy in total. Kidney (bilateral or ipsilateral) 15 Gy in total with no fraction greater than 5 Gy and no more than a 1/2 of one kidney receiving greater than 14 Gy. Chest wall 40 Gy in total and no fraction greater than 12.5 Gy. Liver- mean liver dose < 1500cGy and per QUANTEC
- *Dose schedule*: Patients will receive 3-5 treatments on consecutive weekdays or every other day

Status of Liver Lesion	Fraction #	Total Dose
Max of single liver lesion	3	30-60 Gy
Multiple liver lesions	3 5	30-37.5 Gy 25-30 Gy
Previously irradiated, cirrhotic or significant hepatic impairment	5	25 Gy

Guidelines will be followed and the ASTRO/ACR Practice Guidelines in regard to treatment (not personnel) will be followed

NB: In all circumstances, normal tissue tolerances need to be respected and dose reductions will be acceptable to meet those criteria. Significant hepatic impairment is determined by the radiation oncologist, surgeon and their consultants. Childs-Pugh Class C can be used as a justification for no treatment

but patients with Childs-Pugh Class C can be treated if considered medically appropriate.

4.2.5 Radiosurgery: Spine/Soft tissue

Please note soft tissue lesions are expected to be rare except when they are located in the paraspinal region. If there is a soft tissue metastases is in another location these cases will need to be reviewed by two credentialed radiation oncologists for radiosurgery.

4.2.5a Equipment

Photon (x-ray) beams produced by linear accelerators with energies 4-18 MV will be allowed, preferably using photon beams with energy of 6 MV or less. IMRT or other dose painting techniques are allowed. Proton beams, and other charged particle beams (including electrons, heavy ions) are not allowed. Gamma Knife® or PerfexionTM treatment is not allowed.

4.2.5b Treatment technique

Inverse treatment planning will be employed using isocentric and/or non-isocentric beam arrangements.

4.2.5c Treatment volumes

The goal of treatment planning is to deliver a conformal dose of radiation to the contrast enhancing target volume based on MR or CT images. Treatment volumes will be determined based on correlation of diagnostic imaging with a treatment planning CT scan performed at 1.00 to 1.50 mm slice thickness. Minimal margins of up to 3 mm will be used. The relevant target volumes and critical structures for treatment planning will be contoured by the participating radiation oncologist and/or thoracic surgeon. Both radiation oncologist and thoracic surgeon need to review the target volumes. The preferred image for target contouring is a CT image post-contrast at a minimum of 1.5 mm between image slices with the image obtained at the normal breathing cycle. A CT myelogram can be performed to better delineate the neural structures

4.2.5d Treatment simulation

- The simulation procedure will involve obtaining the CT dataset in the treatment position and during the normal breathing cycle through the region of interest.
- All patients will be simulated in the supine position, head at the superior portion of the treatment/simulation table.
- For cervical and upper thoracic (T5 and higher), immobilization of the head with the neck in mildly extended position is expected
- For other regions of the spine, the patient's head will be in the neutral position or in a position that maintains a comfortable airway
- The CT dataset for treatment planning will be obtained at 1.00 mm to 1.5 mm slice thickness and will be a non-contrast study
- The patient's head and body should remain in the PDP safety zone.

- A contrasted CT scan will be obtained in the treatment position after the non-contrast study has been obtained in a similar fashion as the non-contrasted study if indicated clinically.

4.2.5e Treatment immobilization

Patients must be positioned in a stable supine position capable for reproducibility of positioning and immobilization from simulation to treatment, allowing the patient to feel as comfortable as possible. Positions uncomfortable for the patient should be avoided to prevent unnecessary movement. A prone position is not allowed. A variety of immobilization systems may be utilized including vacuum bag, alpha cradle, or stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the treatment delivery coordinate system. In addition, for cervical spine or cervicothoracic junctional areas, a rigid head and neck immobilization device should be used. Patient immobilization must be reliable enough to achieve the accuracy requirement of image-guidance.

4.2.5f Treatment schedule / time and dose considerations

Time and dose considerations:

- P*rescription isodose*: The dose will be calculated to the 60-100% isodose curve as normalized to the maximum dose. In general, the 60-80% isodose curve is strived for target coverage
- *Coverage*: The target lesion should be covered at least 95% by the prescription isodose curve and 99% should be covered by 90% of the prescription isodose curve
- *Conformity of dose*: Conformity indices $PIV*TIV/TV^2$ should be within 1.00 – 2.00
- *Total dose*: The total dose to the prescription isodose
- *Normal tissue dose limitations*:
    - **For single fraction treatment:** The maximum voxel dose to the spinal cord should not exceed 15 Gy in a single fraction. 10% of the volume (as defined as 6mm above and below the PTV) should be less than 10 Gy in a single fraction. No voxel to the kidney greater than 15Gy with a limit of 6 Gy to 50% of the kidney
    - **For patients who have received prior radiation or are receiving treatment to multiple levels, treatment typically will be fractionated**: The maximum voxel dose to the spinal canal should not exceed 5 Gy in a single fraction and 10% of the volume should not exceed 3 Gy in each individual fraction. Total cumulative dose to the spinal cord should not exceed 15 Gy to 10% of the volume if fractionated treatment is utilized. Attempts to limit dose to the kidney to < 2 Gy per fraction with absolute limit of 50% of the kidney receiving less than 15Gy the dose to the whole lung (bilateral) will be a V20 of < 15%. Esophagus < 27 with no fraction greater than 9 Gy. Heart/ proximal bronchus/trachea/ great

vessels < 30 Gy with no fraction greater than 10 Gy. Brachial plexus < 24 Gy with no fraction greater than 8 Gy

- *Dose schedule*: Radiosurgery treatments will be delivered on consecutive weekdays for one to five fractions (one fraction per day) and delivered per institutional preference (on consecutive days versus several per week)

Status of Vertebral Body	Fraction #	Total Dose
Max of single Vertebral Body	1	12-20 Gy
Multiple Vertebral Bodies/NT limits	3 5	21-30 Gy 25-30 Gy
Previously Irradiated	3 5	21 Gy 25-30 Gy

NB: In all circumstances, normal tissue tolerances need to be respected and dose reductions will be ac

4.3 Erlotinib Treatment Dosage and Administration

Erlotinib (Tarceva®) will be administered per standard of care. Of note, patients with EGFR mutation often require substantially less than the standard dose to achieve efficacy. Thus, while the study recommends a standard starting dose, patients with known intolerance at this dose, but known tolerance with efficacy at a lower dose will be allowed to initiate at that dose. Erlotinib will be taken once per day on an empty stomach (one hour before, or two hours after food).

At the time of enrollment into the study, patients may already be on erlotinib therapy. For these patients, it is recommended (but not required) that erlotinib be discontinued 3 days prior to the initiation of SRS (i.e., if last dose of erlotinib is on a Sunday, SRS can be administered on Thursday). The study recommends that erlotinib be restarted 3 days after the completion of SRS. At the investigator's discretion, erlotinib may be started sooner (or never discontinued) but not later. .

4.4 Toxicities and Dosing Delays/Dose Modifications

Erlotinib is FDA approved for the population being studied and treating clinicians have extensive experience in toxicity management, dosing delays, and dose modifications. As erlotinib is the only FDA approved TKI targeted against EGFR in the United States and no international sites are planned, it is anticipated that most or all patients will have received erlotinib specifically prior to study entry. The study therefore does not demand a specific strategy for toxicity management. Rather, the study refers clinicians to the PI and published guidelines.

4.5 Concomitant Medications/Treatments

Erlotinib does not commonly causes significant interactions with concomitant medications. In theory, CYP3A4 inhibitors may increase erlotinib plasma

concentrations and inducers may decrease erlotinib plasma concentrations. CYP1A2 inducers may decrease erlotinib plasma concentrations. Cigarette smoking is known to decrease erlotinib serum concentrations. While standard practice does sometimes require an increase in erlotinib dosing, this study is open only to patients with the EGFR mutation, who typically are nonsmokers.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

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

4.7 Duration of Follow Up

Patients will be followed until death. See section 6.5 for details.

5.0 DRUG INFORMATION

5.1 Erlotinib (Tarceva®)

5.1.1 Mechanism of Action

The mechanism of clinical antitumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

5.1.2 How supplied

Erlotinib is a tyrosine kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy, and for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. For the present study, it will be supplied by Astellas Pharma at no charge to study subjects.

5.1.3 Dosing and administration

The standard recommended dose of erlotinib for NSCLC is 150mg. However, the inclusion criteria of this study demand presence of an EGFR mutation. Previous studies have demonstrated that patients with this mutation can achieve efficacy with substantially lower dosages with subsequent better tolerance of therapy. Thus, while the recommended dose will remain the FDA approved dose of

150mg, lower doses, down to the previously effective dose, will be permitted. Erlotinib should be taken on an empty stomach, either one hour before or two hours after food. No premedication, hydration, or special storage is required.

5.1.4 Adverse Events Associated with Erlotinib

Standard adverse events associated with erlotinib are described from the PI and are consistent with those observed in clinical care. However, it is notable that patients with previous intolerance to erlotinib are excluded from the study. Therefore, tolerance in this study will likely be higher than that described in the literature.

The most common side effects of erlotinib are rash and diarrhea. Two major trials, the SATURN maintenance trial and the BR.21 2nd line trial allow comparison of patients treated with erlotinib to those treated with placebo. These data are summarized in the prescribing information for erlotinib (see www.tarceva.com), and below.

Table 1 summarizes the SATURN trial, and Table 2 the BR.21 2nd line trial. Both tables summarize AEs occurring more frequently (≥3%) in the single agent erlotinib group then in the placebo group, and in ≥3% or ≥10% of patients in the erlotinib group (SATURN and BR.21, respectively).

TABLE 1

	Erlotinib (n=433)			Placebo (n=445)		
Grade	**Any**	**3**	**4**	**Any**	**3**	**4**
	%	%	%	%	%	%
Rash	49.2	6.0	0	5.8	0	0
Diarrhea	20.3	1.8	0	4.5	0	0
Fatigue	9.0	1.8	0	5.8	1.1	0
Anorexia	9.2	<1	0	4.9	<1	0
Pruritus	7.4	<1	0	2.7	0	0
Acne	6.2	<1	0	0	0	0
Dermatitis Acneiform	4.6	<1	0	1.1	0	0
Dry skin	4.4	0	0	<1	0	0
Weight decreased	3.9	<1	0	<1	0	0
Paronychia	3.9	<1	0	0	0	0

TABLE 2						
	Erlotinib (n=485)			Placebo (n=242)		
Grade	Any	3	4	Any	3	4
	%	%	%	%	%	%
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritis	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Assessment	Pre-study[1]	Post SRS[2]	Q 8 Weeks X 3[3]	Q 6-12 Weeks[4]	Early Termination[5]	At Progression[6]	Follow -up
Informed Consent	X						
History and PE[7]	X	X	X	X	X		X
ECOG Performance Status (Appendix A)	X	X	X		X		
Pregnancy Test	X[8]						
CBC with diff/platelets	X	X	X	X			
Serum chemistries[9]	X	X	X	X			
Liver function tests[9]	X	X	X	X			
Tumor evaluation	X[10]		X[10]	X[10]	X[10]	X[10]	X[12]
Concomitant Meds	X		X		X		
Toxicity Assessment	Continuous during the study						
Blood sample for Veristrat® Assay[11]	X	X[11]	X[11]			X[11]	
Subsequent therapy				X[4]		X[12]	X[12]
Charlson comorbidity index (Appendix B)	X						

See Key to Footnotes on next page.

Key to Time and Events Table

[1] Unless otherwise noted, perform within 2 weeks prior to initiation of SRS or local ablative therapy. CT or PET within 4 weeks prior to the start of therapy

[2]Post SRS or local ablative therapy, pre-erlotinib unless patient enrolled in trial on erlotinib and continuing it through SRS, see section 4.3 (NOTE: this visit can occur on the last day of radiation)

[3]The initial 3 visits post erlotinib initiation will be performed at the enrolling site, and can take place every 8 weeks +/- 1 week; however, the tumor measurements at these visits should take place within 1 week (7 days) prior to the study visit. If patient progresses prior to the end of 6 months, then they will enter long-term follow-up (see section 6.5).

[4] For patients living a distance prohibitive for further travel to the enrolling site, visits after the initial 6 months on erlotinib (or after progression) for clinical care may be performed remotely by the patient's primary oncologist. In this case, records will be requested, specifically including doctors' notes, imaging reports, and CDs of imaging.

[5]This visit will be scheduled when a subject is withdrawn from study therapy prior to progression

[6] At the time of progression, choice of regimen for next treatment will be requested. If patient is not being treated at an enrolling site, these records may be obtained remotely. Imaging reports and images will be requested to ascertain the nature of and duration of response to the next line of therapy, when possible.

[7]Complete medical history at baseline, thereafter, symptom directed history

[8]Serum or urine pregnancy test for women of child bearing potential

[9]Serum chemistries include sodium, potassium, chloride, bicarbonate, magnesium, BUN, serum creatinine, glucose, calcium, total protein and albumin; liver function tests include total bilirubin, alkaline phosphatase, AST, and ALT)

[10]CT or PET scan-use consistent imaging throughout study; NOTE: the X^{10} at progression is there to indicate that progression was diagnosed via a tumor evaluation

[11] Draw 3.5 mL of blood into SST (gold -top) Vacutainer tube Blood for Verstrat® assay at study entry (prior to SRS or local ablative therapy), post SRS or local ablative therapy (and prior to erlotinib, either that day's dose, or prior to initiating erlotinib), at the first visit following SRS, and at the time of progression (if feasible). See section 6.7 for additional information.

[12] See sections 6.5 and 6.9.7.

6.2 Pre-Study Assessments

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. CT or PET scan must be done within 4 weeks prior to the start of therapy. Pre-study assessments include:

- Complete medical history and physical examination (including height and weight)
- ECOG Performance Status (see appendix A)
- Charlson Comorbidity Index (see appendix B)
- Laboratory evaluations: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, magnesium, BUN, serum creatinine, glucose, calcium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, albumin, urine or serum pregnancy test in women of childbearing potential
- Record all concomitant medication(s)
- Tumor evaluation: CT or PET Scan
- Confirmation of EGFR mutation or clinical response to EGFR TKI (see inclusion criteria 3.1.3)
- Toxicity evaluation (for notation of any baseline toxicity) via NCI CTCAE v4.
- Blood sample for Veristrat® assay: Draw 3.5 mL SST (gold -top) Vacutainer tube. See section 6.7 for additional details.

6.3 Treatment Assessments

6.3.1 Post SRS or other Local Ablation

- Symptom directed medical history and physical examination
- ECOG Performance Status (see appendix A)
- Laboratory evaluations: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, magnesium, BUN, serum creatinine, glucose, calcium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, and albumin
- Toxicity evaluation (for notation of any baseline toxicity) via NCI CTCAE v4.
- Blood sample for Veristrat® assay: Draw 3.5 mL SST (gold -top) Vacutainer tube. See section 6.7 for additional details.

6.3.2 Every 8 weeks x 3 for a total of 6 months (or until progression, whichever occurs earliest)

- Symptom directed medical history and physical examination
- ECOG Performance Status (see appendix A)
- Laboratory evaluations: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, magnesium, BUN, serum creatinine, glucose, calcium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, and albumin
- Record all concomitant medication(s) added or changed.

- Tumor evaluation: CT or PET Scan
- Toxicity evaluation (for notation of any baseline toxicity) via NCI CTCAE v4
- Blood sample for Veristrat® assay (at first visit post SRS/local ablative therapy only): Draw 3.5 mL SST (gold -top) Vacutainer tube. See section 6.7 for additional details.

6.3.3 Subsequent Every 6-12 Weeks until Progression

For patients who do not progress within the first 6 months on study, following the formal 6 month follow-up post erlotinib initiation at the site, patients will be assessed per standard clinical practice. Typically, this involves serial physical examination, laboratory and imaging evaluations every 6-12 weeks, but this will be done at the discretion of the treating physician. If the patient does not receive his/her clinical care at a participating institution, doctor's notes, imaging reports, and CDs of images will be requested to confirm time of progression, time of death, and toxicity.

6.4 Evaluation at Progression

At the time of progression on erlotinib, the time of documented progression will be recorded. If feasible, obtain blood sample for Veristrat® assay: Draw 3.5 mL SST (gold -top) Vacutainer tube. See section 6.7 for additional details. At the time of progression, choice of regimen for next treatment will be requested. If patient is not being treated at an enrolling site, these records may be obtained remotely. Imaging reports and images will be requested to ascertain the nature of and duration of response to the next line of therapy, when possible.

6.5 Long-Term Follow-Up

After progression, follow-up of patients will be limited to collecting response rate and PFS to subsequent therapy when possible, and survival status. If the patient does not receive his/her clinical care at a participating institution, doctor's notes, imaging reports, and CDs of images will be requested to confirm response, time of subsequent progression, and time of death. Theses data will be collected every 6 months until death, will be recorded on the electronic case report form (eCRF), and may be requested/collected via telephone.

6.6 Early Termination Visit

The following assessments will be performed, if possible, when a subject is withdrawn from study therapy prior to progression:

- Symptom directed medical history and physical examination
- ECOG Performance Status (see appendix A)
- Record all concomitant medications(s) added and/or changed
- Tumor evaluation — CT or MRI Scan and physical examination.
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, Version 4). Patients who have on ongoing Grade 4 or SAE at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.

6.7 Correlative Studies Procedures: Veristrat®

Blood will be obtained and samples blinded at the following intervals:

- At study entry (prior to SRS)
- Subsequent to completion of SRS/local ablative therapy, but prior to rinitiation of erlotinib or that day's dose of erlotinib
- At the first visit following SRS/local ablative therapy
- At the time of progression (if feasible)

The following collection and processing procedures will be followed:

- Biodesix will provide the investigative site with the materials necessary to complete this process.
- Assign a blinded sample number from the Master Worksheet provided by Biodesix. Complete 3 study identification labels with the blinded number.
- Place 1 label on each of the following provided by Biodesix:
    - 3.5 mL SST (gold -top) Vacutainer tube.
    - Serum Collection Card.
    - Study test request form (TRF), upper right corner.
- Collect venous blood into the 3.5 mL SST Vacutainer.
- Gently invert the SST 5 times and allow the tube to clot in an upright position for 30 minutes at room temperature (approximately 70°Farenheit or 21°Celcius (C).
- Spin the SST in a standard clinical centrifuge at a speed of 1000-1300 gravity (g), or equivalent, for 10-15 minutes. Speed should not exceed 1300 g, and time should not exceed 15 minutes or hemolysis may occur.
- Verify that the serum is light yellow in color. Pink or reddish serum indicates sample has hemolyzed and must be redrawn.
- Without disturbing the clot layer, use a transfer pipette to transfer 2 drops (0.1 mL) of serum to each of the 2 circles on the Serum Collection Card.
- Dispose of SST.
- Close cover of Serum Collection Card and follow shipping instructions. Sample must be shipped within 24 hours, and may be stored at room temperature until shipping.

The following shipment procedures will be followed:

- Place the Serum Collection Card into foil bag and seal.
- Place the foil bag and the completed study TRF into the shipping envelope. Save the yellow copy of the study TRF for placement in the subject's study records.
- Complete the required FedEx® air bill fields, and if shipping on a Friday, check the Saturday delivery box. Remove the sender's copy of the air bill for the subject's study records, and place the remainder of the air bill in the pouch in the shipping envelope.
- Arrange for and confirm FedEx pickup of the package the same day as the sample is prepared for shipping.

Any specimens remaining after protocol-directed studies are complete will be destroyed by Biodesix at the completion of the study.

6.8 Assessment of Safety

Any patient who receives treatment on this protocol will be evaluable for toxicity via NCI CTCAE version 4. Further information on this assessment is provided in the time and events table.

6.9 Assessment of Efficacy

Patients who complete SRS (or other local ablation), receive at least 14 doses of erlotinib, and have their disease re-evaluated at 8 weeks will be evaluable for assessment of the primary objective (PFS). Patients who drop out of the study prior to this point will not be evaluable for the primary objective unless they have received at least 14 doses of erlotinib, and have either clearly progressed or died. If a patient comes off study at any point after 8 weeks without having progressed or died, they will be censored at their last known progression-free date.

6.9.1 Progression free survival

Progression free survival will be the primary endpoint of the study. Progression free survival will be measured from the time of initiation of SRS until the time of progression or death. Lesions that progress on initial TKI therapy will be treated with SRS or other locally ablative maneuver. Because of concern for potential antagonism between erlotinib and radiation as well as safety concerns, erlotinib will be held during SRS. This could potentially allow growth of non-treated, erlotinib-sensitive clones during this period, with later disease control on erlotinib. For this reason, non-treated lesions that progress between the pre-treatment and pre-erlotinib reinitiation evaluations will not be counted as progressive disease unless they also progress on the 1st follow-up imaging while on erlotinib. Further, areas treated with SRS are known to sometimes inflame as a consequence of therapy, with no actual disease progression. In clinical practice, radiologist and radiation oncologist assessment of these lesions are predictive of

long-term control. Therefore, clinician judgment will be used for both protocol and treatment decisions in evaluating whether a lesion treated with SRS that appears larger is actually progressive. In all cases, the same judgment must be used for both evaluation of control on study, and clinical decision making.

6.9.2 Local control rate of SRS treated lesions

As noted above, areas treated with SRS are well known to inflame after therapy. In these cases, the clinical judgment of the radiologist and radiation oncologist will be used to assess the local control of specific lesions. Of note, observation over time may be necessary for definitive assessment of some lesions.

6.9.3 Overall survival

Overall survival will be measured from the time of initiation of SRS until the time of death.

6.9.4 Toxicity of SRS

Toxicity of SRS will be graded by NCI CTCAE version 4.

6.9.5 Toxicity of erlotinib post SRS/local ablative therapy

The toxicity of erlotinib has been well defined in multiple phase III studies. However, two elements are different in this study. First, erlotinib is being used after SRS. While this has been done before in clinical practice, the toxicity has not been systematically assessed. Second, if the therapy is efficacious, patients may spend a longer time on erlotinib and live a longer time, potentially exposing longer-term toxicities that have been masked by previously short PFS and OS.

6.9.6 Veristrat® in EGFR mutated NSCLC

Veristrat® has been shown to be prognostic in untreated patients as well as predictive of both response and survival in EGFR-TKI treated patients, including patients with EGFR mutation. Although change in Veristrat® result from “good” to “poor” has been demonstrated in patients progressing on an EGFR-TKI, the assay has never been evaluated in the context of a therapy seeking to restore systemic sensitivity to a TKI and a “poor” to “good” transition has never been documented. Exploratory analyses of both the good vs. poor signature and individual peaks will be explored at serial time points.

6.9.7 Responses to subsequent therapies

It is possible that the study treatment modulates treatment outcomes to subsequent therapies. For example, ablation of clones resistant to erlotinib may also ablate cells that bear resistance to the chemotherapy later chosen. Therefore, to the extent possible, response rate and PFS to subsequent therapy will be recorded on the electronic case report form (eCRF).

6.9.8 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

Response rate will be assessed for SRS.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

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

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.9.9 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is

added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression".

6.9.10 Evaluation of Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.9.11 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and 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.

6.9.12 Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of the study treatment until the end of treatment provided the confirmation criteria are met. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed > 4 weeks after the criteria for response are first met. If a CR/PR cannot be confirmed the original "response"

should be considered stable disease. The best overall response will be defined according to the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[2] NE=inevaluable

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue until the AE or SAR is resolved or returns to <grade 1 or baseline.

Collected information should be recorded in the Electronic Case Report Forms (eCRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

For any other experience or condition that meets the definition of a serious adverse event (SAE) or SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or serious SARs) must be recorded in the eCRF for that patient within 24 hours of learning of its occurrence. For Affiliate sites, an email must also be sent to the NCCN Project Manager indicating that an SAE or Serious

SAR has been entered into Oncore (email contact will be provided at study start-up).

7.3.3 Reporting

FDA Expedited Reporting requirements for studies conducted under an IND:
If an investigator deems that an event is both a serious SAR AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. If the event occurs at an Affiliate site, the MedWatch form should be faxed to the UNCCN Project Manager at 919-966-4300 along with supporting documentation defining the event and causality. The MedWatch 3500a form can be accessed at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.
(Please be sure and access form 3500a, and not form 3500). UNC, as the Sponsor of the study, will make the final determination regarding FDA submission.

UNC study personnel are responsible for informing the Principal Investigator of the SAE, and, if it is also a serious SAR AND unexpected, for forwarding all MedWatch 3500A forms to the FDA in accordance with 21 CFR 312.32 (for drugs under an IND) and 21 CFR 314.80 (for marketed drugs).

The UNCCN Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs via fax as soon as possible.

IRB Reporting Requirements:
Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Project Manager using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

UNC:

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

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7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of the Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety and Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This is a single arm phase II trial of 40 patients evaluating a novel treatment strategy for EGFR-mutant NSCLC patients who have just progressed on an EGFR-TKI. The primary endpoint of the study will be progression free survival. Secondary endpoints include overall survival, local control rate of sites ablated by SRS, toxicity of SRS, toxicity of erlotinib after SRS, and proteomics based biocorrelates (Veristrat®).

8.2 Sample Size and Accrual

No data exist at this time to define median progression-free survival on chemotherapy, following first-line erlotinib. However, the FDA has approved docetaxel, pemetrexed and erlotinib for second line therapy based on a median

PFS of 1.8-2.9 months, establishing a standard for minimally effective second line therapy.

Study	Regimen	PFS/TTP
Hanna[19]	Docetaxel Pemetrexed	2.9 2.9 (PFS)
BR.21[20]	Erlotinib Placebo	2.2 1.8 (PFS)
Shepherd[21]	Docetaxel Placebo	10.6w 6.7w (TTP)
TAX 320[22]	Doctaxel Vin or ifos	8.5w 7.9w (TTP)

While a PFS that matched the best previously demonstrated second line results would be sufficient to meet the threshold for further study, several factors are worthy of note in considering how such results could be interpreted and utilized. First, both SRS and erlotinib are substantially less toxic than cytotoxic chemotherapy. Second, this therapy would represent an additional option for EGFR mutant patients—after second progression on erlotinib, patients would still be eligible for treatment with standard chemotherapy. Thus, we hypothesize that the proposed treatment strategy will lead to a median progression free survival of at least 3 months.

A median PFS of 3 months implies that at 3 months, 50% of the population will still be progression free (PF). With 40 patients, the following table shows the precision of the 95% confidence interval that will be constructed for the percentage of patients who are PF at 3 months. If the percentage of patients PF at 3 months is 65% the 95% CI will be (48%-79%).

Number of Pts Progression Free at 3 months	3 month PFS (95% CI)
16/40	40% (25%, 57%)
18/40	45% (29%, 62%)
20/40	50% (34%, 66%)
22/40	55% (38%, 71%)
24/40	60% (43%, 75%)
26/40	65% (48%, 79%)
28/40	70% (53%, 83%)

We expect the percentage of patients who are PF at 3 months to be more than 50%, so with 40 patients, if 65% or 70% of patients are PF at 3 months, the exact 95% binomial confidence interval will be sufficiently narrow and suggest that the median PFS is longer than 3 months. An exact binomial test with a nominal 0.05 one-sided significance level will have 80% power to detect the difference between the null hypothesis of 50% PF at 3 months and the alternative hypothesis of 70% PF at 3 months when the sample size is 40.

8.3 Data Analyses Plans

Kaplan-Meier curves with appropriate confidence bands will be used to estimate the primary endpoint of median progression free survival. An exact 95% binomial confidence interval for the percentage of patients progression free at 3 months will be also be constructed, and a one-sided test will be done to see if it significantly higher than 50%. While the primary objective is to estimate median PFS, with 40 patients, we may be able to detect a significant improvement over a null hypothesis of only 50% of patients being progression free at 3 months.

Appropriate descriptive statistics including means, standard deviations, medians, and ranges will be provided for continuous data (ex. proteomics), and proportions will be used to summarize categorical data (ex. control and toxicity rates). Standard Kaplan-Meier curves and Cox proportional hazard models will be used to analyze time to event endpoints (including secondary endpoint of OS).

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

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

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

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

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

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

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

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM.

For Affiliate patients, to register and confirm patient eligibility, please fax registration forms, informed consent, and source documents to 919-966-4300..

9.4 Data Management and Monitoring/Auditing

The CPO of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents

supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six to twelve months depending on Affiliate site participation.

9.5 Adherence to the Protocol

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

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

9.5.3 Other Protocol Deviations/Violations

According to UNC's 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 meets any of the following criteria:

- 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 please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

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

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:

Affiliate Sites:

Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Project Manager. The UNCCN Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:

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

For Institutions Relying on Their Own IRB:

Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

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

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

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

on file until three years after the completion and final study report of this investigational study.

9.8 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 into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

1. D'Angelo SP, Pietanza MC, Johnson ML, et al: Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. J Clin Oncol 29:2066-70, 2011

2. Zhou C, Wu YL, Chen G, et al: Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735-42, 2011

3. J. Wang CZ, Y. Wu, S. Lu, L. Zhang, Y. Zhang, M. Ye, J. Ma, J. Huang, Q. Xiu: OPTIMAL: Phase III Study of First-line Erlotinib Versus Gemcitabine Plus Carboplatin (GC) in Chinese Patients (pts) With Activating EGFR Mutation-Positive Advanced Non-small Cell Lung Cancer (NSCLC). On behalf of the OPTIMAL Investigators. , Chicago Multidisciplinary Symposium in Thoracic Oncology. Chicago, IL, 2010

4. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380-8, 2010

5. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 11:121-8, 2010

6. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-57, 2009

7. Paz-Ares L, Soulieres D, Melezinek I, et al: Clinical outcomes in non-small-cell lung cancer patients with EGFR mutations: pooled analysis. J Cell Mol Med 14:51-69, 2010

8. Das AK, Chen BP, Story MD, et al: Somatic mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) abrogate EGFR-mediated radioprotection in non-small cell lung carcinoma. Cancer Res 67:5267-74, 2007

9. Das AK, Sato M, Story MD, et al: Non-small-cell lung cancers with kinase domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation. Cancer Res 66:9601-8, 2006

10. R. H. Mak ED, A. Muzikansky, J. Kang, N. C. Choi, H. Willers, D. M. Jackman, L. V. Sequist: Thoracic radiation therapy in locally advanced NSCLC patients (pts) with EGFR mutations, J Clin Oncol 28:15s, 2010 (suppl; abstr 7016)

11. Okunieff P, Petersen AL, Philip A, et al: Stereotactic Body Radiation Therapy (SBRT) for lung metastases. Acta Oncol. 45:808-17., 2006

12. Khan AJ, Mehta PS, Zusag TW, et al: Long term disease-free survival resulting from combined modality management of patients presenting with oligometastatic, non-small cell lung carcinoma (NSCLC). Radiotherapy and Oncology 81:163-167, 2006

13. Milano MT, Katz AW, Muhs AG, et al: A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. Cancer 112:650-658, 2008

14. Benedict SH, Yenice KM, Followill D, et al: Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 37:4078-101, 2010

15. Taguchi F, Solomon B, Gregorc V, et al: Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study. J Natl Cancer Inst 99:838-46, 2007

16. Lazzari C, Spreafico A, Bachi A, et al: Changes in plasma mass-spectral profile in course of treatment of non-small cell lung cancer patients with epidermal growth factor receptor tyrosine kinase inhibitors. J Thorac Oncol 7:40-8, 2012

17. Amann JM, Lee JW, Roder H, et al: Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. J Thorac Oncol 5:169-78, 2010

18. Carbone DP SL, Ding K et al.: Serum proteomic prediction of outcomes in advanced NSCLC patients treated with erlotinib/placebo in the NCIC clinical trials group BR.21 trial. J Thoracic Oncol 5:S80; abstract 2030, 2010

19. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-97, 2004

20. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-32, 2005

21. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-103, 2000

22. Fossella FV, DeVore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18:2354-62, 2000

11.0 APPENDICES

11.1 Appendix A ECOG Performance Status

Grade	Definition
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

11.2 Appendix B Charlson Comorbidity Index Scoring System

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.

Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.