Pilot Study of Local Therapies for Oligometastatic Non-Small Cell Lung Cancer harboring Sensitizing EGFR Mutations

PROTOCOL FACE PAGE FOR MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title:	Local Therapies for Oligometastatic Non-Small Cell Lung Cancer (NSCLC) harboring Sensitizing EGFR Mutations
Objectives:	Primary objective: • To assess the safety and tolerability of local treatment of oligometastatic disease combined with tyrosine kinase inhibitor (TKI) therapy • • To determine the feasibility of accruing eligible patients to undergo the proposed treatment plan • To collect preliminary data on the efficacy of the proposed treatment strategy: o Time to progression o Time to death o Local control at site of local therapy o Time on EGFR TKI before a new systemic therapy is required Correlative objectives: • To compare the molecular alterations in the primary lung versus metastatic sites by performing next-generation sequencing (IMPACT) on archived pre-treatment and resected specimens. • To evaluate cell free plasma DNA (cfDNA) as a tumor biomarker for recurrent disease.
Patient Population:	Patients with newly diagnosed, untreated stage IV oligometastatic (≤5 lesions of disease) lung adenocarcinomas harboring sensitizing EGFR mutations: • all sites of disease (including CNS) must be amenable to definitive treatment with a local therapy (as per surgery, interventional radiology and radiation oncology) • all hilar and mediastinal nodal disease to be considered as part of the primary disease and not a metastatic site
Design:	Single-arm, prospective trial: 5 patients will be enrolled at our institution to demonstrate feasibility of both enrolling patients and having them complete all local therapies in a 2 year time frame.
Treatment Plan:	Patients will be placed on EGFR-TKI for their metastatic EGFR-mutant stage IV oligometastatic disease. All patients will undergo induction TKI for 12 weeks. At the conclusion of 12 weeks on erlotinib, patients without disease progression [partial response (PR) or stable disease (SD)] will undergo definitive local treatment to all remaining sites of disease. After local therapy, erlotinib will be resumed until progression of disease (POD) by RECIST criteria.

	Patients who achieve a complete response (CR) at a site of disease, will have the option to forgo local therapy at that site and just continue EGFR TKI. Patients with progressive disease after 12 weeks of erlotinib will be taken off study. • Definitive local therapies include surgical resection, stereotactic radiosurgery, ablation and conventional radiation therapy • After induction TKI (12 weeks), local therapies will be completed sequentially. The expectation is that all local therapies will be completed within 8 months of patient enrollment. • The treating MD will confirm if the patients TKI should be held for 2 days before and restarted within 14 days after each local therapy and otherwise continued. If the treating MD feels that it will be ok for the patient to continue erlotinib during local treatment, this will be allowed per protocol. • If initially symptomatic, a patient may receive a definitive local therapy prior to completion of induction TKI at the discretion of the treating physician. • Patients who have POD at any time will be taken off study and continue conventional systemic treatment and/or local therapies for palliative purposes as per their primary medical oncologist.
Number of Patients:	5 patients for feasibility

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary objective:

- This is a single-arm, single institution trial evaluating a multimodality treatment plan consisting of local therapies and continued erlotinib in patients with stage IV oligometastatic lung adenocarcinoma harboring sensitizing EGFR mutations
- To assess the safety and tolerability of local treatment of oligometastatic disease combined with TKI therapy
- To determine the feasibility of accruing eligible patients to undergo the proposed treatment plan
- To collect preliminary data on the efficacy of the proposed treatment strategy:
  - Time to progression
  - Time to death
  - Local control at site of local therapy
  - Time on EGFR TKI before a new systemic therapy is required

2.3 Correlative objectives:

Correlative objectives:

- To compare the molecular alterations in the primary lung versus metastatic sites by performing next-generation sequencing (IMPACT) on archived pre-treatment and resected specimens.
- To evaluate cell free plasma DNA (cfDNA) as a tumor biomarker for recurrent disease.

3.0 BACKGROUND AND RATIONALE

Lung Cancer

Lung cancer is the most common cancer worldwide, and in the United States, there will be an estimated 224,000 new cases of lung cancer and 159,000 deaths in 2014.[1] Half of all patients with stage IB – IIIA non-small-cell lung cancers (NSCLCs) who undergo curative therapy with surgery and peri-operative chemotherapy die within five years of their initial diagnosis.[2] The majority of patients with NSCLC present with metastatic (stage IV) disease. The 5-year survival rate for patients with stage IV NSCLC is <5%. However, a subset of patients with stage IV NSCLC present with oligometastatic disease, and appear to have a more favorable prognosis.

Local Therapies in Oligometastatic Disease

The limited extent of metastases in the oligometastatic state raises the possibility of definitively treating all site of disease. Oligometastatic disease may represent a separate intermediate disease state where cancers have gained additional genetic alterations that result in metastasis, but have not yet acquired the capability for widespread metastases. Local therapies such as radiation, radiofrequency ablation, and metastatectomy are routinely performed in other cancers such as renal cell carcinoma, sarcoma, and colorectal cancer for oligometastatic disease with excellent disease free survival in a subset of cases. Oligometastatic disease is typically defined as fewer than 5 discrete sites of disease[3-5] although this can vary with different tumor types. The goal of treating oligometastatic disease with local therapies is to render the patient free of disease if the primary tumor is otherwise controlled.

Local Therapies in Oligometastatic Lung Cancer

While local therapies in metastatic lung cancer are typically reserved for palliative purposes, some studies suggest patients with oligometastatic disease treated with local therapies might have improved outcomes.[6-9] Patients who undergo surgical resection and/or radiation therapy of a solitary brain metastasis have a median survival of approximately 40 weeks[10], and the 5-year survival rates range from 10-20%.[11] Follow-up whole brain radiation and/or SRS[12-1415,16] are additional treatment options. In patients undergoing resection of brain metastases from NSCLC, complete resection of the primary lung disease prolongs survival.[11] Local treatment for brain metastases is currently considered standard of care. In patients with an isolated adrenal metastasis (up to 33% patients) and an otherwise curable lung cancer, local therapy of the adrenal lesion can result in long-term survival in up to 25% patients.[17-19]. There is some thought that ipisilateral adrenal metastases actually represent locoregional spread though retroperitoneal lymphatic channels. Guidelines now recommend that in patients with a distant metastasis in a solitary site, such as a brain or adrenal lesion, metastastectomy should be considered in addition to systemic therapy[20]

A recent study by Parikh and colleagues prospectively enrolled 186 patients with oligometastatic non-small cell lung cancer, defined as 5 or fewer distant metastatic lesions at diagnosis, and evaluated patient and disease characteristics associated with improved survival. The number of metastatic lesions and radiologic size of the primary tumor were not associated with overall survival. Eastern Cooperate Oncology Group performance status ≥2 (hazard ratio [HR] 2.43), nodal status N2-3 (HR 2.16), squamous pathology, and metastases to multiple organs (HR 2.11) were associated with a greater hazard of death (all P<0.01). Importantly, patients who received aggressive local treatment to either the primary tumor only (HR 0.64; 95%CI 0.33-1.24; P=0.19) or to both primary tumor and metastatic sites (HR 0.59; 95%CI 0.37-0.95; P=0.03) had improved survival (19 months [95%CI 13-34 months] vs 16 months [95%CI 13-19 months]) compared to patients who received either aggressive treatment to the metastatic sites only or no aggressive treatment.[21]

Rationale for Local Therapies in EGFR-mutant Metastatic Lung Cancer

Sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% Asian patients. The majority of patients with tumors harboring sensitizing EGFR mutations will respond to EGFR TKIs (>70% response rate) with a median progression-free survival of 12 months.[22-27] Patients with EGFR-mutant lung cancer have a unique biology and are clinically characterized not only by improved outcomes with EGFR-TKIs, but also by better results from chemotherapy and surgery compared to their EGFR-wild-type counterparts.[22,28] Prospective studies evaluating EGFR TKIs, including gefitinib, erlotinib, and afatinib, all show a superior radiographic response rate and progression-free survival with TKI compared to standard cytotoxic chemotherapy.[22-26] Even with the development of acquired resistance to TKIs, patients with EGFR-mutant lung cancers have a median survival of 16 months[29] compared to 12 months from initial diagnosis of stage IV disease in unselected patients.[30]

One of the favorable prognostic factors generally used in the selection of patients for metastasectomy includes prolonged progression-free survival, representing patients with slower growing disease.[31-33] Given their relatively indolent clinical course, patients harboring sensitizing EGFR mutations are more likely to benefit from local treatment for oligometastatic disease sites and thus present a unique opportunity to achieve increased long-term survival. Not only do EGFR-mutated patients have a superior prognosis with longer overall survival, but 60% of patients with metastatic EGFR-mutated NSCLC treated with EGFR-TKIs first develop disease progression in their initial sites of disease, lending credence to the concept that upfront local therapy to all sites may prolong progression-free survival. *(unpublished data).*

In a published report, we identified 18 patients who received elective non-central nervous system local therapy (surgical resection, radiofrequency ablation, or radiation), in conjunction with continued EGFR-TKIs.[34] Local therapy was well tolerated with 85% of patients restarting TKI therapy within 1 month. The median time to progression after local therapy was 10 months (95%CI 2-27 months), and medial overall survival from local therapy was 41 months (95%CI 26-not reached). The median time until a subsequent change in systemic therapy was 22 months (95%CI 6-30 months).

Another retrospective analysis by Weickhardt and colleagues described 25 patients, with either an EGFR mutation or an ALK rearrangement, who received a local therapy (stereotactic body radiation therapy in most cases) to oligoprogressive metastases after targeted therapy. After local therapy, the median progression-free survival was 6.2 months with 19 of 25 patients progressing again.[35]

These remarkable outcomes are likely a reflection of a multitude of factors including the natural history of this patient population, continued benefits of TKI therapy even after progression, and the potential benefits of local therapy. Prospective evaluation of local therapy as part of a standard treatment paradigm is warranted to better define the patient population and treatment parameters that could result in improved outcomes, possibly even prolonged disease-free survival.

For locally advanced disease we often give induction chemotherapy prior to surgical resection for a number of reasons including 1) easier tolerability 2) to eliminate micrometastatic disease 3) to achieve a pathologic response and 4) to improve surgical outcomes. This approach has led to an improved median disease-free survival (27 vs 13 months) and median overall survival (37 vs 26 months) compared to surgery alone.[36] We hope to apply this concept to patients with EGFR-mutant oligometastatic stage IV disease using TKI therapy as induction therapy to improve survival outcomes.

Correlative Studies

Intratumor heterogeneity

Large-scale sequencing platforms have revealed extensive genetic heterogeneity between individual tumors that can contribute to treatment failure and drug resistance. Specifically, studies comparing mutational profiles of primary tumors and associated metastatic lesions or local recurrences have provided evidence of intratumor heterogeneity.[37-40] Intratumor heterogeneity within primary tumors and associated metastatic sites has not been systematically characterized by next-generation sequencing in lung cancer.

This study affords an opportunity to investigate intratumor heterogeneity by comparing mutation profiles on matched primary and metastatic resected tissue specimens. We will use a next generation sequencing based genotyping assay (MSK IMPACT) that performs massively parallel sequencing of all exons corresponding to 341 cancer genes. The sequencing data will be analyzed for base mutations, insertions, deletions, copy number alterations and genomic rearrangements in all target genes.

Cell-free plasma DNA as a biomarker for recurrence

Studies suggest that highly sensitive genotyping assays can detect mutations in cell-free plasma DNA (cfDNA) from patients with cancer, potentially providing a non-invasive method to identify and track intratumoral genetic alterations.

Several studies have demonstrated a prognostic value of the total level of tumor cfDNA, with high levels being associated with shorter survival.[41,42] Quantitative changes in tumor cfDNA during a patient's treatment course may be used as a marker to monitor response to therapy.[43] Quantification of cfDNA could be used as a tumor marker that tracks with response to therapy, but also as a biomarker whose presence could predict recurrent disease prior to radiographic or clinical recurrence. To investigate this, we will obtain serial assessments of cfDNA during routine venipunctures as per protocol to capture changes in cfDNA during treatment.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm, single institution trial evaluating a treatment plan consisting of local therapies and continued erlotinib in patients with stage IV oligometastatic lung adenocarcinoma harboring sensitizing EGFR mutations. At least five patients will be enrolled at our institution to demonstrate feasibility of accrual and successful completion of treatment over a 2 year time period. After demonstrating feasibility of this approach, a multicenter efficacy study will be planned. Patients will be enrolled at the start of TKI for their untreated EGFR-mutant stage IV oligometastatic disease. All patients will receive “induction” TKI for 12 weeks. Patients who respond (PR/SD) will undergo definitive local treatment to all remaining measurable sites of disease. After local therapy, TKI will be resumed until progression of disease (POD) by RECIST criteria. Patients who achieve a complete response (CR) will not be mandated to have local therapy performed, and TKI will be continued. Patients with progressive disease during these 12 weeks such that complete local therapy is no longer possible will be removed from the study.

The start of the timeline of prtocol assessments begins when the patient starts erlotinib, regardless if that was before or after registration on the study. Patients would be required to follow the schedule of assessments from the timepoint at which they were registered on study. Retroactive pill compliance will not ned to be completed for these patients. Patient dosing compliance will only be required once the patient is registered to the protocol.

4.2 Intervention

All patients will receive erlotinib 150mg daily as induction therapy, with dose reductions allowed based on patient’s symptoms. If patients have a PR or SD, definitive local therapies will be performed on all remaining measurable sites of disease. Definitive local therapies include surgical resection, stereotactic radiosurgery, radiofrequency ablation and conventional radiation therapy and will be determined by respective departments (surgery, interventional radiology and radiation oncology). Specifically, whole brain radiation therapy (WBRT) and hepatic artery embolization will not be included as definitive local treatment options. Per the discretion of the treating MD, a patients erlotinib may be held for 2 days before and up to 14 days after each local treatment, but otherwise will be continued for the duration of the trial until progression of disease.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Erlotinib

Commercially available erlotinib will be obtained. All tablets are round, white, film-coated and bi-convex with no imprint. Erlotinib should be stored at room temperature, not above 25°C (77°F). Additional information regarding erlotinib can be found in the Tarveva® Package Insert.

5.2 Surgery

Resectability of the primary lung lesion will be assessed by a thoracic surgeon, and resection of metastases will be evaluated by the appropriate surgical service, i.e. neurosurgery for CNS lesions, surgical oncology for adrenal lesions, thoracic surgery for lung or intrathoracic lesions, etc. A complete resection should be deemed achievable in order to consider surgical resection of a site of disease, and the appropriate extent of resection (anatomic, limited resection, etc.) will be at the discretion of the surgeon, so long as ideally an R0 resection of the lesion can be obtained (with the exception of bone, where an R0 resection is difficult to confirm). Either minimally invasive or open approaches may be utilized at the discretion of the surgeon. Resection of the lung primary should entail an anatomic resection if possible.

5.3 Radiation Therapy

The optimal radiotherapeutic dose and technique will be determined by the radiation oncologist. Stereotactic body radiation therapy (SBRT) is the preferred technique wherever technically feasible. However, conventionally fractionated radiation therapy will also be acceptable for lesions or sites deemed suboptimal for SBRT. The minimum biologically effective dose (BED) to all sites treated with RT is $48Gy_{10}$.

5.3.1 SBRT

In general, SBRT should be recommended, prescribed and delivered according to prevailing institutional standards for that anatomic site. In the lung, SBRT should be utilized if there is no evidence of intrathoracic nodal metastasis. Preferred regimens include 50Gy in five fractions, 48Gy in four fractions, or 54Gy in three fractions, in order to achieve a BED of at least $100Gy_{10}$, but lower-BED regimens may be chosen in cases of large tumor volume or proximity to critical structures such as the esophagus.

Brain metastases must be amenable to treatment with stereotactic radiosurgery (SRS) or to hypofractionated stereotactic radiotherapy. For SRS, treatment regimens will typically entail a dose of 16-22Gy in a single fraction. For tumors too large for SRS, hypofractionated stereotactic radiotherapy to a dose of 30Gy in 5 fractions is acceptable.

For other disease sites, recommended SBRT regimens include 50Gy in five fractions (particularly for liver metastases), 24Gy in one fraction (primarily for bony metastases), and 27Gy in 3 fractions. The minimum acceptable SBRT regimen is 30Gy in 5 fractions, corresponding to a BED of $48Gy_{10}$.

With the exception of brain SRS which may be performed using a frame-based approach, all SBRT should be performed with on-board CT guidance at the time of each fraction. Where appropriate, motion management techniques should be applied as per prevailing institutional standards of care. Normal tissue constraints as per current institutional guidelines should be respected.

5.3.2 Conventionally fractionated radiotherapy

Where SBRT is not deemed feasible due to the size or anatomic location, conventionally fractionated radiotherapy is acceptable. The recommended regimen is 45Gy in 15 fractions, with 40Gy in 10 fractions as an acceptable alternative. 30Gy in 10 fractions would not be acceptable, since this is not considered a definitive treatment dose and the BED of this regimen is $<48Gy_{10}$. 3D-conformal radiation techniques, or intensity-modulated radiation therapy (IMRT) should be utilized, with the potential exception of small bony metastases in the extremities where no significant advantage from conformal techniques would be expected. In general, the PTV should be a minimum of a 1.0cm expansion from the GTV, with additional expansions to account for respiratory motion where appropriate.

5.4 Radiofrequency ablation

The optimal ablative therapy will be determined by the Interventional Radiologist. A safe approach will be determined with the expectancy of completely (A0) ablating the targeted tumor.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Newly diagnosed metastatic lung adenocarcinoma (recurrent or de novo) harboring sensitizing EGFR mutations (L858R, exon 19 deletion, G719A, L861Q, S768I, exon 19 insertions) with oligometastatic disease (≤5 discrete lesions of disease irrespective of location, inclusive of the primary lesion):
  - all sites of disease must be amenable to definitive treatment with a local therapy (surgical resection, stereotactic radiosurgery, ablation and conventional radiation therapy) as determined by surgery, interventional radiology and radiation oncology
  - all intrathoracic lymph nodes (including hilar, mediastinal, and supraclavicular nodal disease) are considered 1 discrete lesion.
  - Each brain metastasis is included as a distinct lesion.
  - Patients already started on erlotinib are eligible as long as their sites of disease are determined to be eligible for definitive local therapy by consensus of the principal investigators within 12 weeks of the patient first taking erlotinib.
- Lung adenocarcinoma histology confirmed at MSKCC.
- Available archived tissue to perform molecular analysis
  - Patients without available archived tissue can have repeat biopsies to determine EGFR status as per standard clinical care guidelines
- Age 18 years or older
- Karnofsky Performance Status ≥ 70%
- Adequate bone marrow, liver and renal function, as specified below:
  - Absolute Neutrophil Count (ANC) ≥ 1.5×10^9/L
  - Hemoglobin ≥ 8 g/dL
  - Platelets ≥ 100×10^9/L
  - Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except for patients with documented Gilbert's Syndrome)

- AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present
- Serum creatinine ≤ 1.5 x upper limit of normal or creatinine clearance ≥ 60ml/min for patients with creatinine levels above institutional normal.

- For women of child-bearing potential, negative pregnancy test within 14 days prior to starting treatment
- Men and women of childbearing age must be willing to use effective contraception while on treatment and for at least 3 months thereafter

6.2 Subject Exclusion Criteria

- Treatment with erlotinib prior to developing metastatic disease
- Patients with activating but not sensitizing mutations (exon 20 insertions, EGFR T790M)
- Malignant pleural effusion or pleural disease
- Leptomeningeal disease
- Any site of disease that is not amenable to definitively local therapy including surgery or radiation therapy
- Women who are breastfeeding or pregnant
- Concurrent malignancies other than non-melanoma skin cancer that require active ongoing treatment.
- Any medical co-morbidities that would preclude surgery or radiation therapy

7.0 RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator or research team at Memorial Sloan Kettering Cancer Center will identify potential research participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation of the diagnosis of advanced, oligometastatic NSCLC and confirmation of the presence of a sensitizing EGFR mutation within the patient's tumor. Potential subjects that meet these basic criteria will be referred by their treating physician to the investigator/research staff of the study. Minorities and women are well represented in the thoracic oncology clinics, and we expect that they will well represented in the trial accrual. The principal investigator, Helena Yu, MD , will be available to all patients for further questions and information through a contact number which will be provided on the consent form itself.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patients during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes or processes, for example advertisements, payments to participants, reimbursement plans, etc.

8.0 PRETREATMENT EVALUATION

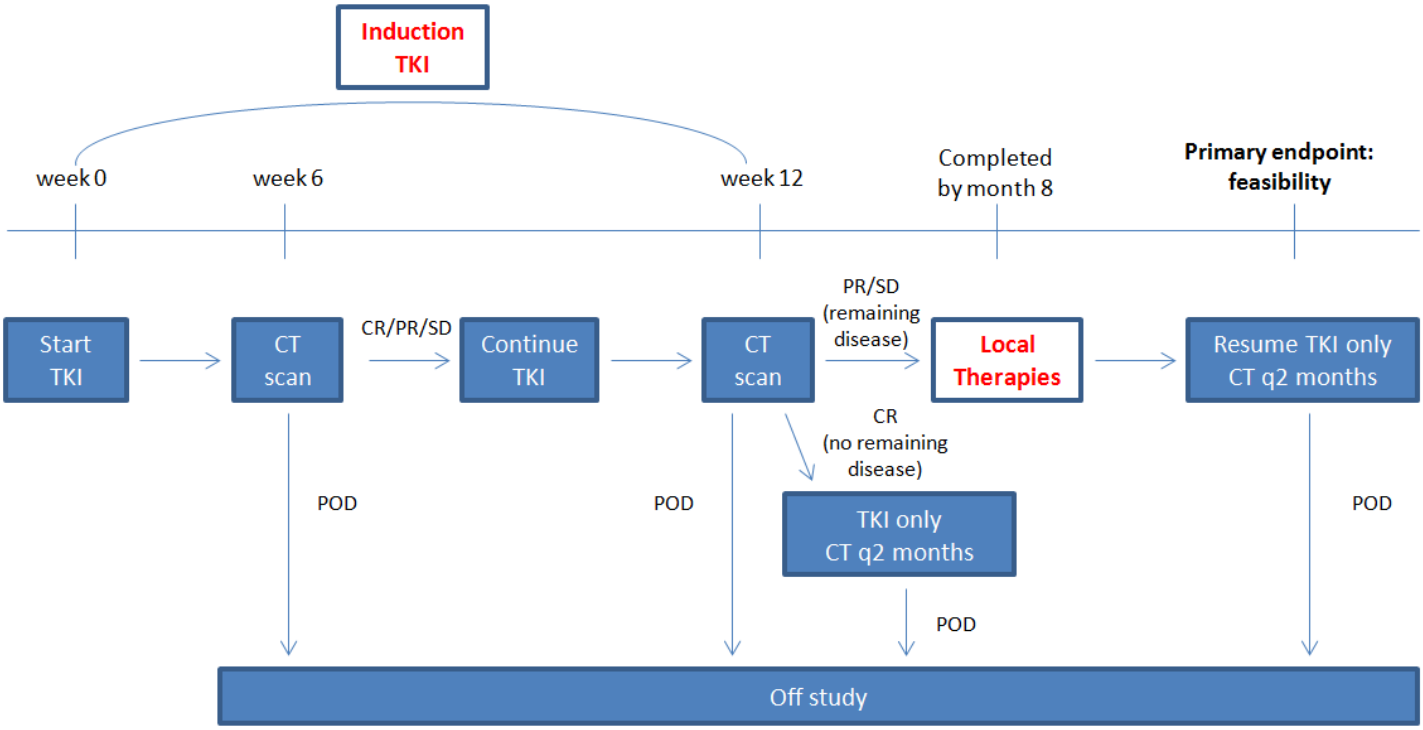
All aspects of the screening evaluation should be completed within four weeks of starting treatment unless otherwise noted.

- Documented presence of lung adenocarcinoma harboring a sensitizing *EGFR* mutation (L858R, exon 19 deletion, G719A, L861Q, S768I, exon 19 insertions) within the patient's tumor. This may be done at any time prior to starting treatment.
- Medical history
- Baseline tumor assessment with PET/CT and Brain MRI (or CT head with contrast) to assess full extent of disease. Other comparable radiologic studies (MRI) can be used as medically appropriate. Radiographic assessments will be done by RECIST 1.1.
- Physical examination, complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height. Height may be documented at any time prior to starting treatment.
- 12-lead electrocardiogram (ECG) within 3 months prior to starting treatment
- Performance status by KPS or ECOG
- Serum pregnancy test
- Complete blood count with differential
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST)
- Surgical, Interventional Radiology and/or Radiation Oncology consult to confirm all disease sites can be treated definitively with a local therapy (surgery or radiation therapy). Patients can be enrolled and started on erlotinib prior to being seen by surgical and/or radiation oncology consults. The entire team will discuss each case to review the most appropriate local therapies, and the patient will be seen by the necessary services.

9.0 TREATMENT/INTERVENTION PLAN

This is a single-arm trial evaluating the feasibility of enrollment and successful completion of a treatment plan consisting of local therapies and continued TKI in patients with stage IV oligometastatic lung adenocarcinoma harboring sensitizing EGFR mutations. Patients will be enrolled at the start of erlotinib for their untreated EGFR-mutant stage IV oligometastatic disease. All patients will start with "induction" erlotinib for 12 weeks. If patients have already started erlotinib, they are still eligible for this protocol as long as they can articulate a clear erlotinib start date, have baseline scans to review and enrollment and consultations by surgical oncology and/or radiation oncology are completed within 12 weeks of the patient first taking erlotinib. The start of the timeline of protocol assessments begins when the patient starts erlotinib, regardless if that was before or after registration on the study. Patients would be required to follow the schedule of assessments from the timepoint at which they were registered on the study. Patients who respond (PR/SD) will undergo definitive local treatment to all remaining sites of disease with the goal of rendering the patient free of disease. Patients who achieve a complete response (CR) can continue TKI without any local

therapy. Patients with progression of disease and are no longer candidates for local therapies will be taken off study. Erlotinib will be resumed after local therapies until progression of disease (POD) by RECIST criteria.



- Definitive local therapies include surgical resection, stereotactic radiosurgery, ablation and conventional radiation therapy
- After induction TKI (12 weeks), local therapies will be completed sequentially with the expectation that all local therapies will be completed within 8 months of patient enrollment.
- Per the discretion of the treating MD, a patients erlotinib may be held for 2 days before and restarted 2-14 days after each local therapy and otherwise continued in between therapies.
- No local therapy will be mandated to any original disease site that has completely regressed during induction erlotinib. Proceeding with local therapy in this situation is at the discretion of the treating physicians.
- For symptomatic purposes, a patient may receive a definitive local therapy prior to completion of induction erlotinib per treating physician.
- Patients who have POD during induction erlotinib will not receive local therapies unless otherwise necessary for palliative purposes.

After induction TKI, patients will be monitored for POD and safety/tolerability with repeat imaging, physical exam, and laboratory tests every 8 weeks for 1 year. These evaluations must be performed at MSKCC sites to ensure consistency of results and facilitate the

collection of specimens for correlative analyses. After 1 year, the patient will be monitored in the same manner every 12 weeks until POD.

In order to better understand feasibility, on a monthly basis, we will obtain a list of all patients with positive EGFR mutant test results by routine molecular testing. We will cross reference this list with patients that are seen by thoracic medical oncology and identify the subset that has stage IV disease.

We will proceed with enrollment without accrual limitations until 5 patients have successfully completed all intended local therapies. To be deemed feasible, at least 5 patients will need to be enrolled, complete local therapy within two years of the study opening to accrual.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Study Calendar

	Baseline[a]	**Induction TKI**			**Induction TKI**			**Induction TKI**			**Induction TKI**			**Local Therapy (surgery and/or radiation)**	**TKI only**	**End of Study**[h]
		W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W13 to W32	W33 to end of study	
Erlotinib		X	X	X	X	X	X	X	X	X	X	X	X	X[a]	X	
Exam	X	X		X			X						X	X[e]	X[e]	X
CBC	X			X			X						X	X[e]	X[e]	X
CMP	X			X			X						X	X[e]	X[e]	X
Pregnancy Test[b]	X															
PET[i]	X															
CT							X[c]						X[c]	X[c,e]	X[c,e]	X[c]
Brain MR or CT	X															
ECG	X															
Tissue analysis	X													X		X
Research Blood	X												X	X[e]	X[e]	X
Local therapy Consult and Procedures	X													X[f]	X[g]	

[a] Erlotinib may be held for 2 days before and up to14 after each local therapy, otherwise continued as tolerated in between local therapies
[b] Serum pregnancy test is required prior to treatment for women of childbearing potential
[c] CT chest and all other areas of disease as clinically indicated including repeat brain MRI/CT with contrast if brain metastases, with a +/- 14 day window.
[d] Erlotinib may be held for 2 days before and 2-14 after each local therapy, otherwise continued as tolerated in between local therapies
[e] To be completed every 8 weeks (± 2 weeks) etc until 1 year on study and then every 12 weeks thereafter indefinitely until POD
[f] Surgical, radiation oncology and radiology procedures will be performed as planned during the screening period
[g] standard follow up with surgery, radiation oncology and radiolology

[h] End of study visit to be performed within 30 days ± 7 days of treatment discontinuation
[i] PET scan to be performed unless contra-indicated, and then a CT or MRI can be performed.
[j] Week 1

[k] All assessments completed during the 12 week TKI induction phase are to be performed per protocol with a ± 7 day window.

10.2 Treatment Modifications

- For symptomatic purposes, a patient may receive a definitive local therapy prior to completion of induction TKI
- Erlotinib may be held for longer than 14 days after a local therapy if medically necessary.

10.3 Correlatives

10.3.1 MSK-IMPACT testing on primary and metastatic tumor specimens

Next-generation sequencing (IMPACT) will be performed on all resected specimens to compare the molecular alterations in metastatic sites versus primary lung site.

10.3.2 Cell free plasma DNA as biomarker for recurrent disease

Plasma will be obtained at regular intervals including screening, week 12 of TKI induction, every 8 weeks until 1 year on study and then every 12 weeks thereafter. Five cc's of peripheral blood will be drawn at a time of standard of care venipuncture, with plasma separated within 5 hours of collection. Cell free DNA will be extracted and frozen at -80C until analyzed. After samples are obtained, they will be sent to Dr. Marc Ladanyi's laboratory for analysis.

11.0 TOXICITIES/SIDE EFFECTS

Local Therapy:

Patients will be consented separately for each respective local therapy received.

Toxicity grading will be performed in accordance with NCI CTCAE, version 4.0. For safety and adverse event reporting, see section 17.0

Erlotinib:

Toxicities with erlotinib that are *likely* (>20%) include:

- Fatigue
- Rash
- Diarrhea
- Decreased appetite
- Nausea/Vomiting

Toxicities with erlotinib that are *less likely* (<20%) include:

- Cough
- Shortness of breath
- Infections
- Mouth sores (mucositis)
- Abdominal pain
- Conjunctivitis (inflammation of the eye)
- Gas, heartburn or upset stomach
- Hair loss or thinning
- Fever
- Fingernail/toenail changes and/or irritation of skin around nails
- Possible cracking of skin, especially of fingers and toes
- Increased body hair growth, or eyelash/eyebrow changes
- Dehydration, when you body does not have enough water/fluid as it should, caused by diarrhea and/or vomiting

Side effects that are *rare, but serious* include:

- Pneumonitis (inflammation of the lung)
- Acute renal failure
- Stevens-Johnson syndrome (a severe skin rash)
- Liver failure
- GI bleeding/perforation (bleeding or a hole that develops in the intestine)

Radiotherapy:

Side effects from radiotherapy vary depending on dose, technique, and anatomic site. In general, side effects of radiotherapy that are common (>20%) include:

- Fatigue
- Dermatitis
- Decreased appetite
- Hair loss (only in the area of the radiation treatment)

Toxicities from radiotherapy that are less common (<20%) include:

- Nausea/vomiting
- Diarrhea
- Pneumonitis
- Esophagitis
- Chest wall pain (when undergoing high-dose lung radiotherapy)
- Decreased bone density in the radiated area, which may lead to fracture
- Cough

Side effects that are rare, but serious depend on the site being treated. These include:

- Brain: Seizures, radionecrosis, memory or other cognitive impairment

- Lung: Respiratory failure leading to oxygen dependence or ventilator support, hemoptysis
- Liver: Liver failure
- Spine: Myelopathy
- Abdomen/pelvis: Bleeding or perforation of the stomach or intestines

Surgery:

Side effects from surgery vary considerably based on surgical site. Patients will be consented separately for any surgical procedure. Side effects or complications depend on site of surgery. Common risks and side effects related to surgery in general include:

- Bleeding
- Infection
- Postoperative pain

Ablation:

Side effects from ablation vary considerably based on ablation site. There is a risk of injury to nearby structures or organs. Other possible side effects include:

- Bleeding
- Infection
- Postoperative pain

If an ablation is done in the lung, there is a risk of pneumothorax, or lung collapse. Sometimes a chest tube is required to a lung collapse.

11.1 Management of Erlotinib Related Toxicities

Erlotinib dose modifications will are to be made according to the criteria outline in Table 11.1 for toxicities which are felt to be related to erlotinib.

Table 11.1: Erlotinib Dose Modification Criteria

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic, general (except for what is noted below)*	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is grade ≤ 1, then resume treatment at same dose level, or dose level -1, at the discretion of the investigator	Withhold dose until toxicity is grade ≤ 1, then resume treatment at same dose level, or dose level -1, at the discretion of the investigator
Pneumonitis (in the absence of other causes of pulmonary infiltrates/dysfunction)	Withhold until at baseline. Can resume treatment at same dose at discretion of investigator. If recurs, discontinue permanently.	Withhold until at baseline. Can resume treatment at same dose at discretion of investigator. If recurs, discontinue permanently.	Discontinue treatment, do not retreat.	Discontinue treatment, do not retreat.
Diarrhea	Continue at same dose level. Initiate therapy with loperamide.	Continue at same dose level. Initiate therapy with loperamide.	Initiate therapy with loperamide. Withhold until toxicity is grade ≤ 2. Resume treatment at same dose level or dose level -1 at discretion of investigator.	Initiate therapy with loperamide. Withhold until toxicity is grade ≤ 2. Resume treatment at same dose level or dose level -1 at discretion of investigator.
Rash	Continue at same dose level. Supportive symptom management.	Continue at same dose level. Supportive symptom management. If rash persists or worsens over 14 days, reduce by 1 dose level.	Reduce by 1 dose level. Supportive symptom management and initiate supportive symptom management. If rash persists of worsens over 14 days, interrupt erlotinib until resolution to ≤ grade 2, and resume dose level -1 or -2 at discretion of investigator.	Withhold until toxicity is grade ≤ 2. Initiate supportive symptom management. Discontinue permanently or restart at dose level -2 at discretion of investigator.

11.2 Anti-diarrheal Therapies

Antidiarrheal medications may be introduced if symptoms occur. Previous erlotinib studies have shown that the frequency and severity of diarrhea rarely hindered administration of erlotinib and could be managed with loperamide. The recommended dose of loperamide is 4mg at first onset, followed by 2mg every 2-4 hours until diarrhea-free for 12 hours.

11.3 Anti-rash Therapies

Rash or dermatosis can occur within the first several days of treatment with erlotinib in many patients and has been noted to diminish in severity despite continued treatment. Patients should be informed that skin toxicity is expected during treatment with erlotinib. Skin toxicity can take the form of dry skin, rash, acneiform eruption, and hair and nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. Patients will be encouraged to use an alcohol-free emollient cream or ointment to moisturize dry areas of the body twice a day after therapy with erlotinib is initiated. Patients will also be encouraged to use a titanium dioxide or zinc oxide based sunscreen product on sun exposed areas daily. Patients with any skin toxicity will be referred to dermatology for management. Recommended treatments may include topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with topical therapy. For more severe cases, oral corticosteroids may be administered. Patients who fail to respond to these measures may have erlotinib interrupted, dose reduced or discontinued.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Radiographic Response by RECIST

A PET-CT and brain MRI or head CT with contrast will be performed at baseline to demonstrate all known areas of measurable disease. The baseline study will occur no more than 4 weeks prior to erlotinib administration. An alternative imaging test, including MRI or CT, can be used in patients with contraindications to the radiographic contrast media used.. All patients must have ≤ 5 discrete lesions of disease.

Tumor response will be assessed using RECIST 1.1. The same method (CT scan recommended) and the same technique (i.e. with or without contrast) should be used to characterize each identified and reported lesion at baseline and serially as per protocol. If an appropriate imaging study is done early for any reason (i.e. hospitalization), it can be used for disease assessment. A designated radiologist/physician will be responsible for interpretation of the study imaging according to RECIST 1.1.

All measurable lesions, up to a maximum of 5 lesions total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Definitions of response in target and non-target lesions are described in Table 12.1 and 12.2 below. Table 12.3 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions.

Table 12.1: Evaluation of target lesions	
Complete Reponse (CR):	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the diameters of the target lesions
Progressive disease (PD):	At least a 20% increase in the sum of the diameter of the target lesions or the appearance of one or more new lesions
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Table 12.2: Evaluation of non-target lesions	
Complete Reponse (CR):	Disappearance of all non-target lesions
Incomplete response/Stable disease (SD):	Persistence of one or more non-target lesions
Progressive disease (PD):	Appearance of one or more new lesion and/or unequivocal progression of existing non-target lesion

Table 12.3: Combinations of responses			
Target lesions	**Nontarget lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. All patients who receive at least one dose of treatment with erlotinib will be evaluable for toxicity and outcomes. Patients who discontinue early should return within 30 days of the last dose of the study drugs for a follow up evaluation. Any assessments listed for the final visit as per the study calendar will be performed at that time.

Patients will be withdrawn from the study therapy should they experience any of the following:

- Intolerable or persistent grade 3 or 4 toxicities with erlotinib
- Disease progression (defined by RECIST 1.1) to an extent that makes local therapy impossible per the respective treating physician. Pathological confirmation is not required unless clinically indicated.

Other reasons for study discontinuation include, but are not limited to:

- Change in patient eligibility
- Clinical deterioration or non-compliance with the defined treatment plan leading to inability to complete all local therapies or continue erlotinib
- Protocol violation
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Lost to follow-up
- Death

14.0 BIOSTATISTICS

14.1 Primary Objective

The primary objective of this study will be to determine the feasibility of accrual and completion of the proposed treatment strategy of induction EGFR-directed tyrosine kinase inhibitor therapy followed by local therapies in a 2 year time frame in patients newly diagnosed with oligometastatic lung cancer. The treatment strategy will be deemed feasible if at least five patients are enrolled, respond to induction TKI therapy, and successfully complete all protocol-directed local therapy within 2 years. At least five patients will need to complete local therapy within 2 years of the study being open to accrual for the primary endpoint to be met. We are choosing to initially perform a small feasibility study to ensure that we will be able to identify sufficient eligible subjects to proceed with further investigation of this study concept. We will proceed with enrollment without accrual limitations until 5 patients have successfully completed all intended local therapies. We will assess accrual after the study is open for 2 years. We will be noting the number of patients enrolled that are needed in order to have 5 patients successfully complete local therapy within the 2 year time.

14.2 Secondary Objective

We will collect information on the following efficacy measures and report them at the patient level

- time to progression following enrollment
- time to progression following completion of local therapy
- time to death
- local control at site of local therapy
- time on TKI before a new systemic therapy is required

Safety and Tolerability

Toxicity grading will be performed in accordance with NCI CTCAE, version 4.0 during every clinical visit as per protocol. Adverse events will be reported at the patient level.

14.3 Correlative Objective

The objectives below are exploratory in nature. We will perform the following statistical analyses, understanding that they are hypothesis-generating only.

MSK-IMPACT testing on primary and metastatic tumor specimens

MSK IMPACT testing will be performed on matched metastatic tumors and primary lung tumors. The molecular aberrations detected will be compared in a descriptive fashion.

Cell free plasma DNA as biomarker for recurrent disease

cfDNA will be measured during patients' treatment course and plotted over time, both individually and as summary statistics (median, range).

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

This is a single-arm, non-randomized study.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/patientsafety/dsm-guidelines/page1

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The Data and Safety Monitoring Committee (DSMC) reports to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible. 5 patients will be enrolled in this study. Patients eligible will be 18 years of age or older with a KPS of 70% or greater. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion

4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side-Effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Benefits: The addition of definitive local therapies has the potential to prolong progression free survival and improve the overall survival compared to standard treatment with erlotinib. Patients who progress on treatment can still receive standard, second-line systemic therapies and/or can participate in an alternative clinical trial.

Costs: Patients will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The patient/patient's insurance will be billed for erlotinib and all local therapies as a part of the patients standard treatment course. CLIA-certified mutation testing (i.e. *EGFR* mutation by fragment analysis, Sequenom or standard sequencing) will be billed to the patient/patient's insurance. Research bloods and any other mutation testing that is not required as part of the patient's standard of care will not be billed to the patient/patient's insurance.

Alternatives: The alternative to this trial would be treatment with erlotinib monotherapy at the standard, FDA approved dose of 150mg orally daily, without local therapies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC), the FDA, and/or other governmental agencies) may review patient records as required.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring committee established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1

This protocol is not an Industry or Cooperative group protocol.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

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