Protocol Number: 2012-0618
Protocol Title: A randomized phase II study assessing the efficacy of local consolidative therapy for non-small cell lung cancer patients with induced oligometastatic disease
Protocol Version: 13

Lead Institution: MD Anderson Cancer Center	1515 Holcombe Blvd. Houston, TX 77030
Principal Investigator:	Chad Tang, M.D. Radiation Oncology MD Anderson Cancer Center 1515 Holcombe Blvd Unit 1202 Houston, TX 77030 713-563-2300 (phone) 713-563-1521 (fax) Email: CTang1@mdanderson.org
Co-Principal Investigators:	Stephen Swisher, M.D. Thoracic Surgery
	John Heymach, M.D., Ph.D. Thoracic/Head & Neck Medical Oncology
MDACC Collaborators:	
Radiation Oncology	Mary Frances McAleer, M.D.., PhD Joe Chang, M.D., PhD Zhongxing Liao, M.D Steven Lin, M.D., PHD Michael O'Reilly, M.D. James Welsh, M.D., PhD
Thoracic/Head & Neck Medical Oncology	George Blumenschein, M.D. Lauren Byers, M.D. Frank Fossella, M.D. Don Gibbons, M.D., PhD Faye Johnson, M.D., PhD Charles Lu, M.D. Anne Tsao, M.D. Jianjun Zhang, M.D., PhD
Neurosurgery	Jeffrey Weinburg, M.D.
Thoracic & Cardiovasc Surgery	Wayne Hofstetter, M.D. Reza Mehran, M.D. David Rice, M.D. Jack Roth, M.D. Ara Vaporciyan, M.D. Garrett Walsh, M.D.
Urology	Jose Karam, M.D.
Biostatistician:	J. Jack Lee, M.S. Ph.D Mike Hernandez, M.S.
Pathology:	Ignacio Wistuba, M.D.
Multi Center Coordinator	Aileen Mapps, M.S. MD Anderson Cancer Center 1515 Holcombe Blvd. Unit 1422 713-563-2543 (Phone) Email: Aileen.Mapps@mdanderson.org

University of Colorado	
Principal Investigator:	Brian Kavanagh, M.D. Radiation Oncology University of Colorado Denver Department of Radiation Oncology Anschutz Cancer Pavilion Campus Mail-Stop: F-706 1665 Aurora Court Aurora, CO 80045 720-848-0154 (Phone) Email: brian.kavanagh@ucdenver.edu
London Health Sciences Centre	
Principal Investigator:	David Palma, M.D. London Regional Cancer Program London Health Sciences Centre 790 Commissioners Road East London, Ontario, Canada N6A 4L6 Phone: 519-685-8650 Fax: 519-685-8627 E-mail: David.Palma@lhsc.on.ca
Collaborators	A. Rashid Dar, M.D. Radiation Oncology George Rodrigues, M.D. Radiation Oncology Brina Yaremko, M.D. Radiation Oncology Edward Yu, M.D. Radiation Oncology Brian Dingle, M.D. Medical Oncology Walter Kocha, M.D. Medical Oncology Sara Kuruvilla, M.D. Medical Oncology Michael Sanatani, M.D. Medical Oncology Mark Vincent, M.D. Medical Oncology Jawaid Younus, M.D. Medical Oncology Richard Inculet, M.D. Surgical Oncology

Table of Contents

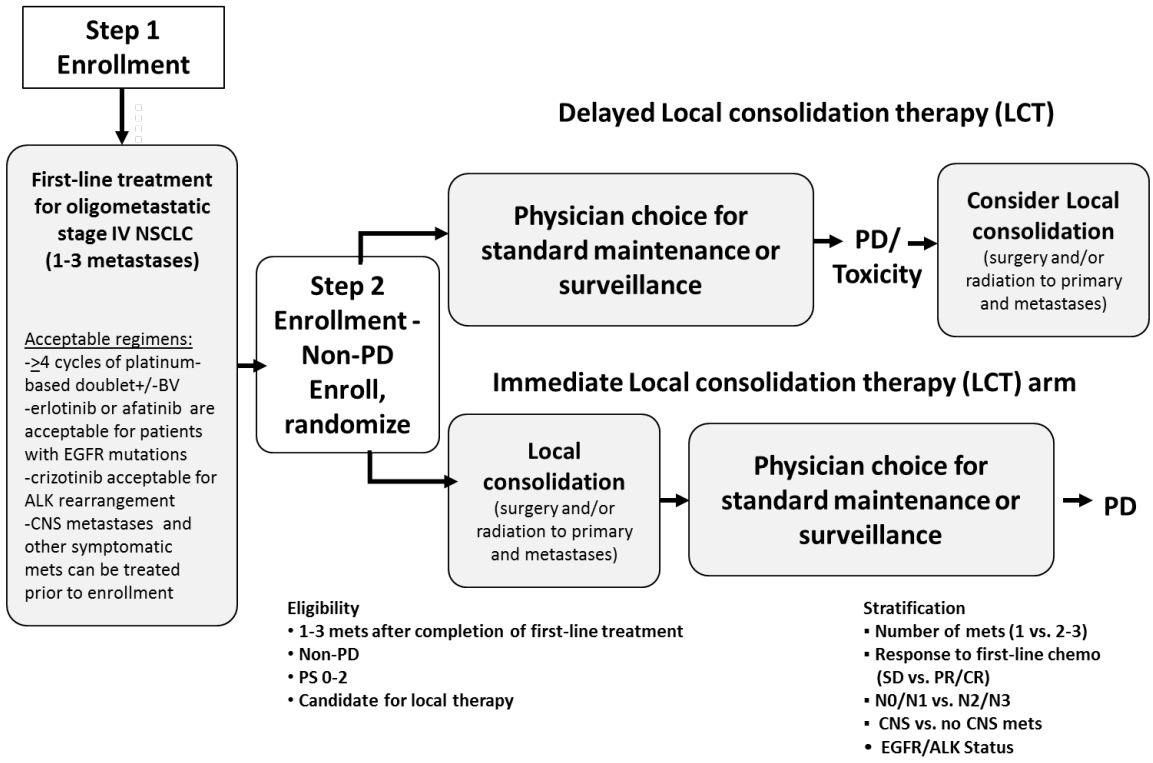
1.0 Objectives……3
2.0 Background and Rationale……..4
3.0 Patient Eligibility…….6
4.0 Treatment Plan…….8
5.0 Symptom Assessment……14
6.0 Optional Procedures……..14
7.0 Statistical Considerations……..15
8.0 Evaluations of Outcome of Interest……...16
9.0 References…….10

Appendix A: Timeline of evaluations before, during and after treatment

Appendix B: MD Anderson Symptom Inventory (MDASI)

Appendix C: Biomarker Analyses

Appendix D: Blood-based biomarkers: collection, processing, and storage of plasma, serum, and peripheral blood mononuclear cells (PMBCs).



Study schema. Oligometastatic (1-3 metastases) NSCLC patients with non-progressive disease (PD) after first line therapy will be randomized to immediate local consolidation therapy (LCT) arm vs. delayed/no LCT arm of primary and metastases. **Crossover of treatment arms is allowed for disease progression or toxicity, at the treating physician's discretion (see Off-Study Criteria below).**

1 OBJECTIVES

1.1 Primary Objectives

The primary objective of this study will be to:
Determine whether oligometastatic NSCLC patients with no disease progression after first line therapy have prolonged progression free survival (PFS) when treated with local consolidation therapy (LCT) of residual disease (radiation or surgery) followed by maintenance or surveillance as per physician choice) compared with no LCT.

1.2 Secondary Objectives

The secondary objectives of this study will be to:

- Determine the overall survival
- Safety/tolerability of LCT
- Time to progression of prior metastatic lesions
- Time to appearance of new metastases (CNS vs. extra-CNS, treated lesion vs. new site)
- Quality of life

1.3 Study Design

This is a Phase II open-label study in NSCLC patients with oligometastatic disease (defined here as 1-3 observable metastases after the completion of chemotherapy) who have no evidence of disease progression after standard first-line therapy (4-6 cycles of platinum-doublet chemotherapy, with or without bevacizumab; erlotinib or crizotinib alone or in combination with other regimens are also acceptable options for patients with tumors known to bear a known EGFR activating mutation (for erlotinib or afatinib) or EML4ALK fusion (for crizotinib). Patients will be enrolled either prior to completing 4 cycles of induction

chemotherapy (step 1 enrollment) or after the completion of at least 4 cycles of chemotherapy (step 2 enrollment). In either case, they will be randomized during Step 2 to the "immediate LCT" arm consisting of LCT followed by either surveillance or maintenance therapy at the discretion of the treating physician, compared to delayed/no LCT. When undergoing LCT (in either arm), patients will receive consolidative therapy with either radiotherapy or surgery for all residual lesions (primary and metastases). The choice of the specific consolidative therapy will be made by the treating physician(s). Consultation with a multidisciplinary team including a radiation oncologist and thoracic surgeon is encouraged.

2. BACKGROUND AND RATIONALE

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the United States and worldwide. An estimated 221,130 new cases of lung cancer were diagnosed in the US in the year 2011 leading to approximately 156,940 deaths in the United States alone[1]. Non-small cell lung cancer (NSCLC) accounts for almost 80% of newly diagnosed cases. Lung cancer deaths in the US surpass those resulting from breast, prostate, and colon cancers, and its incidence continues to rise. Only 16% of these patients in whom lung cancer develops live 5 years or more after the diagnosis is made. Despite substantial effort in developing methods for early diagnosis and treatment of lung cancer in the last two decades, currently at the time of diagnosis, more than 80% of patients present with locally advanced unresectable or metastatic disease and their chance to be cured by current oncology practice is low.

At presentation, the median survival for patients with advanced disease defined as inoperable Stage 3 or 4 non-small-cell lung cancer (NSCLC) is 10-12 months, with a one-year survival of 35 to 45%[2]. Most patients with inoperable NSCLC are candidates for palliative chemotherapy consisting of standard induction therapy with 4 to 6 cycles of a platinum-based chemotherapy doublet, per American Society of Clinical Oncology ASCO[3] and European Society for Medical Oncology guidelines (ESMO)[4].
In 2006, bevacizumab received FDA approval as an initial therapy for advanced NSCLC in patients with non-squamous histology on the basis of Study ECOG 4599[5]. Approval was based on improvement in overall survival (OS) for the combination of bevacizumab, carboplatin and paclitaxel (BCP) for 6 cycles, followed by maintenance bevacizumab, as compared with the platinum doublet alone. This triplet regimen is now recommended by the National Comprehensive Cancer Network for patients with advanced, non-squamous NSCLC and has become one of the standards of care in that setting[6].

Recent randomized phase III studies have established that for patients with tumors bearing known activating EGFR mutations, first line treatment with an EGFR tyrosine kinase inhibitor such as gefitinib or erlotinib prolongs PFS and results in higher objective response rates compared with standard chemotherapy alone [7,8].Erlotinib is now FDA-approved for the treatment of first-line NSCLC patients bearing EGFR mutations.

For a number of years, there has been interest in subclassifying those patients with metastatic disease, and attempting to elucidate those patients that will develop multiple sites of metastases quickly with early death (so-called "polymetastatic" disease) vs. patients that maintain a limited burden of metastases and thus may benefit from local treatment ("oligometastatic" disease).[9,10] The purpose of this study is to compare two approaches (LCT vs. no LCT) in patients that have metastatic oligometastatic NSCLC that responds to upfront chemotherapy, to assess if local therapy can lead to improved outcomes in this select patient cohort.

2.2 Local treatment of oligometastatic disease

There are several studies supporting the use of ablative therapy in the setting of oligometastatic disease. Salama et al. performed a prospective study examining the results of radiation dose escalation in patients with one to five sites of metastatic disease with any histology, all with a life expectancy of >3 months. The starting dose was 8 Gy x 3 fractions, and the protocol-specified maximum dose was 20 Gy x 3 fractions. In an interim analysis of 29 patients with 56 metastatic lesions, the authors found a response rate of 59%, and 21% of patients did not have progression following treatment. In those patients that did

progress, this progression was amenable to further local treatment in 48% of patients.[11] In the final analysis, the authors confirmed that patients with 1 to 5 metastases could be safely treated to multiple body sites and could thus benefit from hypofractionated, "ablative" radiation doses in this setting.[12]

Several retrospective studies have also examined ablative therapy in the oligometastatic setting in patients with NSCLC. Khan et al. retrospectively analyzed the results of 23 patients with oligometastatic disease (1-2 sites) treated with systemic and locoregional treatment. Eighteen of 23 patients had stage III disease in the thorax, and the brain was the most common metastatic site (14/23 patients). At a median follow-up of 17 months (28 months for surviving patients), the median survival was 20 months, and the 5- and 10-year overall survival rates were approximately 40%[13]. In a study from the European Institute of Oncology, the authors found that of 10 patients treated with a solitary metastasis who were evaluated with PET imaging, the median overall survival was 26 months, with a median time to progression of 20 months[14]. In a study from MD Anderson Cancer Center examining 84 patients with newly diagnosed synchronous solitary brain metastasis, the authors found that the 1/2 year survival rates were 50/16%, with a median survival time of 25.6 months for patients that had Stage I intrathoracic disease[14]. Similarly, Bonnette et al. found a median survival of 12 months in 103 patients with solitary brain metastases that underwent surgical resection from 1985-1998[15].

2.3 Maintenance therapy

There are a number of phase III studies supporting the use of maintenance therapy in NSCLC resulting in indications in patients who have not shown progression of disease after 4 or more courses of platinum containing combination therapy. There are two categories of maintenance, continuation maintenance in which, after the combination therapy, one of the drugs is continued; and switch maintenance in which another agent not part of the combination therapy is used as maintenance[17]. Presently, two drugs are FDA approved for switch maintenance, pemetrexed and erlotinib, while bevacizumab is approved as continuation maintenance. Therefore, these three drugs are recommended, but not required, as maintenance therapy in this study. Phase III studies have also demonstrated clinical benefit, in terms of prolonged PFS, for docetaxel[18] and gemcitabine[19] as switch maintenance, and pemetrexed as continuation maintenance[20]. Several of these studies are detailed below. Currently, there is no single standard maintenance approach. Switch maintenance, continuation maintenance, or surveillance are all considered standard of care options and physician choice is typically based on several factors including tumor histology and mutation status, performance status, and symptom burden.

2.3.1 Switch maintenance:

Pemetrexed. In the JMEN study, after four cycles of a platinum plus either gemcitabine, docetaxel or paclitaxel, patients were randomized 2:1 to pemetrexed (500mg/m2) or placebo[21]. At the time of progression, patients in the placebo arm received therapy at the discretion of the treating physician. In all patients, progression free survival (PFS) was 4.3 vs. 2.6 months (P<0.0001) and overall survival of 13.4 vs,. 10.6 months (p<0.0001). The benefits were more pronounced in the non-squamous patients with 4.5 vs. 2.6 months PFS and 15.5 vs. 10.3 months OS. There was no benefit seen in the patients with squamous histology. Grade 3 fatigue was seen in 5% and 1% (p<0.001) and neutropenia 3% vs. 0% (P = 0.0006) of patients receiving pemetrexed and placebo respectively. Treatment caused discontinuation was 5% vs. 1%. On the basis of this study, pemetrexed was approved as maintenance in patients who had received platinum doublets without progression after 4 cycles of therapy in patients with non-squamous histology.

Erlotinib In the SATURN study, patients treated with 4 cycles of platinum doublets without progression were randomized 1:1 to either erlotinib 150mg/day or placebo. A total of 889 patients were randomized with PFS 12.3 vs. 11.3 weeks (HR 0.71, p < 0.0001) erlotinib vs. placebo respectively. Median OS was 12.0 vs. 11.0 (HR = 0.81, p = 0.0088). In a subset analysis, 49 patients with mutated EGFR had a much longer PFS (HR = 0.10, p<0.0001) but similar OS (HR = 0.83 p = 0.68). However, 16/24 in the placebo arm received erlotinib the majority of whom have not had an event thereby complicating the assessment. The patients with wild type EGFR had improved PFS (HR = 0.78, p=0.0185) and OS (HR = 0.77, p=0.024) with erlotinib. Among those with stable disease at randomization (n=487), the HR was 0.72 (p=0.0019)

and median OS was 11.9 and 9.6). However, patients with PR or CR (n=394) have OS (HR = 0.94, p=0. 618). Patients with squamous pathology (n=360) had PFS HR =0.76 CI, 0.60-0.95) but OS was not statistically significant (HR0.86 CI, 0.68-1.10). It is notable that patients with both mutated and wild-type EGFR both had statistically significant improved overall survival[22]. Based on these results, erlotinib was approved by the FDA for use in patients without progression of disease after platinum-based therapy.

In the ATLAS study, the potential to gain benefit from the addition of erlotinib to bevacizumab compared to bevacizumab alone was assessed. The endpoint was PFS, and the study closed early when the study endpoint was reached. There were 373 patients receiving the single agent and 370, the doublet with PFS 4.6 and 4.3 months (HR 0.71, p=0.0006) and OS 13.7 and 12.9 months (0.92 p=0.5604) [23]. Therefore, bevacizumab is an appropriate option for patients due to its PFS benefit.

2.3.2 Continuation maintenance

Bevacizumab The Phase III study (ECOG 4599) randomized patients to either carboplatin-paclitaxel-bevacizumab or carboplatin-paclitaxel[5]. Patients who received 6 cycles of bevacizumab plus chemotherapy without progression continued on single-agent bevacizumab until progression. Median OS was 12.3 months for patients on the bevacizumab plus chemotherapy arm compared with 10.3 months for patients receiving carboplatin plus paclitaxel (HR 0.79; 95% CI: 0.67 to 0.92; p = 0.003). One-and 2-year survival rates were 51% and 23% for the Sandler regimen, compared with 44% and 15% for the chemotherapy-only regimen. The RR was 35% (133/381) for patients on bevacizumab and 15% (59/392) for patients on chemotherapy only (p < 0.001). On the basis of these data, bevacizumab was approved for use in chemonaive non-squamous advanced NSCLC when combined with carboplatin and paclitaxel with the option to continue maintenance bevacizumab for an indefinite period of time. Maintenance bevacizumab is approved as continuation therapy.

Pemetrexed Preliminary results from the Paramount Phase III study were reported in 2011 at the ASCO oral abstract session[20]. Patients with advanced chemonaive non-squamous NSCLC who had not progressed after 4 courses of induction cisplatin plus pemetrexed were randomized 2:1 to receive pemetrexed maintenance or placebo. The primary objective was PFS. 939 patients were enrolled, and 529 patients were randomized with 359 receiving pemetrexed and 180 patients receiving placebo. Median PFS was 4.1 months vs. 2.8 months pemetrexed and placebo respectively (p=0.00006). Benefit was seen across all subgroups by stage, gender, smoking status and pathology subtype. There was no statistical difference in the Health-related Quality of Life Assessment (EQ-5D) between the two arms. However, there was a statistically significant larger percentage of SAEs 8.9% vs. 2.8%. The following were statistically more prevalent in the treatment arm: grade 3 or 4 fatigue was 4.2% vs. 0.6%, anemia 4.5% vs. 0.6% and neutropenia, 3.6% vs. 0%.

3. Patient Eligibility

3.1.1 Inclusion Criteria

The following inclusion criteria must be met for entry into the study.

Step 1 Enrollment

3.1.1.1 The patient has a diagnosis of pathologically confirmed NSCLC by tumor biopsy and/or fine-needle aspiration. Mixed tumors will be categorized by the predominant cell type.

3.1.1.2 The patient has a diagnosis of American Joint Committee on Cancer (AJCC) 7th Edition stage IV NSCLC.

3.1.1.3 Three or less metastatic lesions (not sites).

3.1.1.3.1 The metastatic lesions will be counted as follows: each **lesion** (including a satellite nodule) will individually be counted as one, and intrathoracic lymph node involvement (defined here as hilar, mediastinal, or supraclavicular nodes, N1-N3) will collectively be counted as one. In addition, patients can receive treatment to CNS lesions or other symptomatic lesions requiring urgent local therapy prior to randomization, but these lesions will be counted towards the total number after chemotherapy, and patients will

only be eligible if there are remaining sites amenable to local therapy after up-front systemic therapy.

3.1.1.4 Standard induction chemotherapy planned defined as:
1) At least 4 cycles of platinum doublet chemotherapy for metastatic disease (with or without bevacizumab),
2) if the patient is known to be EGFR mutation positive, erlotinib, afatinib, or gefitinib for ≥3 months, or
3) for patients with known EML4-ALK fusions, crizotinib for ≥3 months

Step 2 Enrollment and Randomization

3.1.1.5 The patient has a diagnosis of pathologically confirmed NSCLC by tumor biopsy and/or fine-needle aspiration. Mixed tumors will be categorized by the predominant cell type.

3.1.1.6 The patient has a diagnosis of American Joint Committee on Cancer (AJCC) 7th Edition stage IV NSCLC.

3.1.1.7 Completion of standard induction chemotherapy planned defined as:
1) At least 4 cycles of platinum doublet chemotherapy for metastatic disease (with or without bevacizumab),
2) if the patient is known to be EGFR mutation positive, erlotinib, afatinib, or gefitinib for ≥3 months, or
3) for patients with known EML4-ALK fusions, crizotinib

Note that it is not mandatory to check EGFR mutation or EML4-ALK status prior to entry, but patients that receive options 2 or 3 should have had these molecular tests performed.

3.1.1.8 Less than or equal to three metastatic lesions and no evidence of disease progression based on RECIST criteria. Note that patients that had >3 metastatic lesions in Step 1 may be eligible for enrollment in Step 2 if the number of metastatic sites is reduced to three or less.

3.1.1.9 The patient's ECOG performance status is ≤ 2 at study entry.

3.1.1.10 The patient must be a suitable candidate for LCT (radiotherapy and/or surgery) to every site of disease, as determined by the treating physician(s). Consultation with a multidisciplinary team, including a medical oncologist, radiation oncologist, and thoracic surgeon, is encouraged but not required.

3.1.1.10.1 Concurrent chemoradiation is permitted as consolidative therapy. The following concurrent therapies are permitted: Tyrosine kinase inhibitors (i.e., erlotinib) – can be delivered with both hypofractionated (≥3 Gy per fraction) and standard fractionated radiation therapy (<3 Gy per fraction); platinum-based chemotherapy – standard fractionated radiation therapy (<3 Gy per fraction)

3.1.1.10.2 Bevacizumab will not be permitted within 2 weeks of the initiation of the radiation therapy course

3.1.1.10.3 Treatment to central nervous system lesions, such as the brain or spine (prior to first line systemic therapy), or symptomatic lesions requiring urgent palliative radiation, is permitted prior to randomization, in which case the patient would be randomized to treatment of other metastatic sites or the primary sites (based on the disease remaining after first-line treatment). These treated lesions should be counted towards the total number of metastases at the time of enrollment.

3.1.1.11 The patient is >/= 18 years of age.

3.1.1.12 The patient has signed informed consent.

3.1.1.13 Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for six (6) months after discontinuation of the study drugs. Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation, hysterectomy or bilateral oophorectomy. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately. The patient, if

a man, agrees to use effective contraception or abstinence for the duration of study participation and for six (6) months after discontinuation of the study drugs.

3.1.2 Exclusion Criteria of Enrollment, Steps 1 and 2 and randomization

A patient meeting any of the following criteria is not eligible to participate in this study:

3.1.2.1 The patient has a history of uncontrolled angina, arrhythmias, or congestive heart failure.
3.1.2.2 Patients with a history of malignant pleural effusions are not eligible. Pleural effusions considered by the investigator too small for a diagnostic thoracentesis are permissible.
3.1.2.3 The patient is pregnant (confirmed by serum b-HCG if applicable) or is breastfeeding.
3.1.2.4 Presence of significant third space fluid which cannot be controlled by drainage
3.1.2.5 The patient has cognitive impairments such that appropriate informed consent cannot be obtained or that he/she cannot participate in required study activities per the opinion of the treating physician.

3.2 Informed Consent Process

We will follow the Office of Clinical Research SOP 04: Informed Consent Process. Written or electronic informed consent will be obtained by the research team after confirming patient eligibility. Informed consent for this study may only be obtained by the Principal Investigator or an assigned designee. This delegation will be included in a protocol delegation log that will be signed by the site's PI.

This study will allow non-English speaking subjects to be enrolled. Verbal Translation Preparative Sheet (VTPS) will be used if a translated consent form is not available in the subject's language. The consent form will be translated into the language of the subject after 2 or more occurrences.

Informed Consent Forms for enrolled patients and for patients who are enrolled but not eligible to receive study treatment (screening failures) will be maintained at the study site. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participating institutions must ensure that the method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirements.

4.0 Treatment Plan

Prior to randomization, eligible patients will have received 4-6 cycles of induction chemotherapy, erlotinib or afatinib (for patients with known EGFR mutations) or crizotinib (for patients with known EML4-ALK fusion) without evidence of RECIST progression. They will be registered and then randomized in a 1:1 fashion to either immediate or no/delayed LCT. All patients will be followed until progression of disease is documented or two years after randomization, whichever comes first. Patients with metastases involving the brain or spinal cord, or metastatic lesions causing symptoms requiring palliation (e.g., bone, soft tissue) may be treated with surgery or radiotherapy prior to the completion of induction chemotherapy (randomization).

The following imaging studies are suggested after first-line therapy to assess the number of sites: 1) imaging of the brain with either a magnetic resonance imaging (MRI) scan (preferred) or a CT scan of the brain with contrast, and 2) systemic imaging with a positron emission tomography/computed tomography (PET/CT) scan or a CT scan of the chest/abdomen/pelvis with contrast. Other studies, such as a bone scan, and aspiration of pleural fluid, are at the treating physician's discretion.

4.1 Induction chemotherapy

Prior to randomization, induction chemotherapy will consist of 4-6 cycles of platinum doublet therapy, erlotinib (for patients with known EGFR mutations) or crizotinib (for patients with known EML4-ALK fusion) for at least 3 months. Either cisplatin or carboplatin in combination with pemetrexed, docetaxel, gemcitabine, vinorelbine, or paclitaxel at the discretion of the treating physician can be used. Bevacizumab or cetuximab may be included with chemotherapy. Maintenance therapy may also be used prior to enrollment provided that 4-6 cycles of platinum doublet treatment has been given. The patient must have received active therapy (doublet chemotherapy, maintenance therapy, erlotinib for EGFR mutation positive patients, or crizotinib for patients with known EML4-ALK fusion) within 12 weeks prior to enrollment.

4.2 Immediate LCT (local consolidation therapy) Arm

Patients who undergo LCT will have ablation of all residual local and metastatic sites of disease by surgery and/or radiation therapy. The optimal form of LCT will be determined by the treating physician(s). Consultation with a multidisciplinary group including a medical oncologist, thoracic surgeon and radiation therapist is encouraged. After the completion of LCT the patient will be treated with surveillance or maintenance treatment as determined by medical oncologist and described below.

4.2.1 Delayed/No LCT Arm – LCT given at the time of progression or toxicity after maintenance therapy or observation

Prior to treatment with maintenance therapy, we recommend adequate hematologic function as defined by an absolute neutrophil count (ANC) >/= 1,500/mm^3, platelet count >/= 100,000/mm^3, WBC >/= 3,000/mm^3, and hemoglobin >/= 9 g/dL within 3 weeks of study entry. We also recommend adequate hepatic function as defined by a total bilirubin level </= 1.5 X the upper limit of normal (Serum bilirubin >/= 1.5x Upper Limit of Normal in the setting of known Gilbert's disease is allowed), and alkaline phosphatase, AST and ALT </= 2.5 X the upper limit of normal or </= 5.0 x ULN if liver metastases are present.

Currently, there is no single standard maintenance approach and treatment is typically chosen based on clinical factors and tumor features (e.g., histology and mutation status). Patients randomized to this arm will receive maintenance therapy (switch or continuation), or surveillance, based on physician choice. Pemetrexed, bevacizumab, crizotinib (for ALK-mutation positive patients) or erlotinib are recommended as acceptable maintenance agents but other agents may be used at physician discretion.

4.2.2 Surgery

Surgical control of primary and metastatic sites of disease may include control of either or both sites of disease as determined by the multidisciplinary group (medical oncologist, radiation oncologist, and surgeon).

4.2.2.1 Primary Site

Surgical resection can be performed by open thoracotomy, video assisted thoracoscopy or robotic assisted thoracoscopy as determined by the surgeon as long as all residual disease can be resected.

Surgery of the primary site may consist of a lobectomy, sleeve resection, wedge resection or pneumonectomy as determined by the attending surgeon based on the operative findings. The type of resection should provide complete removal of the primary lesion with negative gross margins and microscopic margins (if possible). Limited resection is allowed if negative gross margins can be achieved. Documentation of microscopic margins (bronchial and vascular) by frozen section at surgery is not mandatory but encouraged.

Lesions found to have direct extension into parietal pleura or chest wall should be resected if possible with an en-bloc chest wall resection. Similarly, lesions with direct extension to pericardium or diaphragm

should have an en-bloc resection of these structures if possible with an attempt to achieve negative gross margins.

A complete mediastinal lymph node sampling is encouraged. For right-sided lesions, this includes 2R, 4R, 7, 8 and 9. For left-sided lesions, this includes 4L, 5, 6, 7, 8 and 9.

4.2.2.2 Metastatic Sites

Surgical resection of metastatic sites can be performed by open thoracotomy, video assisted thoracoscopy/laparoscopy or robotic assisted thoracoscopy/laparoscopy as determined by the surgeon as long as all residual metastatic disease can be resected with grossly negative margins. In the case of brain metastases, a postoperative MRI should be performed to confirm that a gross total resection has been achieved. Metastatic sites of disease can be controlled by a combination of radiation therapy and surgery if clinically indicated and agreed to by the multidisciplinary team (i.e., surgery and follow-up radiotherapy for CNS lesion).

4.2.3 Radiation Therapy

Radiation therapy will be delivered using external beam radiation, with either 2D/conventional techniques, three-dimensional conformal therapy, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS) or proton beam therapy (PBT), at the discretion of the treating radiation oncologist.

4.2.3.1 Radiation Simulation

Patients will be simulated on a CT scanner (for fractionated radiotherapy or SRS when MRI contraindicated) or using volumetric MRI (for SRS) and immobilized based on the site of disease. Immobilization devices will be at the discretion of the treating radiation oncologist. Typical immobilization devices include a head and neck mask for metastatic sites in this region, an upper body cradle for disease in the thorax, and a lower body cradle for disease in the abdomen, pelvis, or lower extremities. A stereotactic head frame or Aquaplast mask will be used for SRS. Four-dimensional CT scanning will be utilized at the treating radiation oncologist's discretion, to assess for internal motion.

4.2.3.2 Definition of Target Volumes

Target volumes will be approved by the treating radiation oncologist, using the information obtained through clinical examination, radiologic images, the simulation planning study, and histologic specimens. When feasible and necessary, the patient's diagnostic images (CT scan, MRI study, or PET/CT imaging) will be fused with the simulation scan to delineate the suggested target volumes below.

Gross Tumor Volume (GTV) – All known disease detected by the above methods, including nodal disease.

Internal Gross Tumor Volume (iGTV) – GTV plus internal motion, if 4D scanning is obtained at the time of simulation.

Clinical Target Volume (iCTV) – iGTV plus the region at risk for microscopic spread. This target volume will be added at the physician's discretion, given that all patients in this study will have metastatic disease and thus the utility of accounting for microscopic spread is limited.

Planning Target Volume (PTV) – iGTV or iCTV plus a margin to account for patient movement and daily setup error.

Organ at Risk Volumes (OAR) – Delineation of the pertinent organs at risk, to include the lung, heart, esophagus, spinal cord, kidney, and liver.

Table 1. Summary of Suggested OAR Dose Constraints for Standard Fractionation Regimens (<3 Gy per fraction)

Target	Dose Constraint with Standard Fractionation
Brainstem	Maximum Dose <54 Gy
Optic Nerve/Optic Chiasm	Maximum Dose <54 Gy
Retina	Maximum Dose <45 Gy
Total Lung	V20<40% Mean Lung Dose<20 Gy
Liver	40%<50 Gy
Kidneys (both)	1/3<20 Gy
Esophagus	Dmax<70 Gy 50%<50 Gy
Heart	50%<30 Gy 40%<40 Gy
Spinal Cord	Maximum dose 45 Gy
Brachial Plexus	Maximum dose <60 Gy

The dose constraints for hypofractionated regimens will be adjusted based on the number of fractions. Suggested dose constraints for four, ten, and fifteen-fraction regimens are listed below.

Table 2. Summary of Suggested OAR Dose Constraints for four-fraction regimens

Organ	Volume	Dose ((Gy (RBE))
Esophagus	<= 1 cc	35 (Gy (RBE) (8.8 (Gy (RBE)/fx)
	<= 5 cc	30 (Gy (RBE) (7.5 (Gy (RBE)/fx)
Brachial Plexus	Any point	<40 (Gy (RBE)
	<= 1 cc	35 (Gy (RBE) (8.8 (Gy (RBE)/fx)
	<= 5cc	30 (Gy (RBE) (7.5 (Gy (RBE)/fx)
Trachea	<= 1 cc	40 (Gy (RBE) (8.8 (Gy (RBE)/fx)
	<= 10 cc	

		30 (Gy (RBE) (7.5 (Gy (RBE)/fx)
Main bronchus and bronchial tree	<= 1 cc	40 (Gy (RBE) (10 (Gy (RBE)/fx)
	<= 10 cc	35 (Gy (RBE) (8.8 (Gy (RBE)/fx)
Heart	<= 1 cc	40 (Gy (RBE) (10 (Gy (RBE)/fx)
	<= 10 cc	35 (Gy (RBE) (8.8 (Gy (RBE)/fx)
Whole Lung (Right & Left, subtracting GTV)	V20 (GY (RBE)	<20% (of volume)
	V10 (GY (RBE)	<30%
	V5 (GY (RBE)	<50%
Major vessels	<= 1 cc	40 (Gy (RBE) (10 (Gy (RBE)/fx)
	<= 10 cc	35 (Gy (RBE) (8.8 (Gy (RBE)/fx)
Skin	<= 1 cc	40 (Gy(RBE) (10 (Gy(RBE)/fx)
Chest wall	<= 10 cc	35 (Gy(RBE) (8.8 (Gy(RBE)/fx)
Spinal cord	<=50 cc	35 (Gy(RBE) (7.5 (Gy(RBE)/fx)
	<= 1 cc	20 (Gy(RBE) (5 (Gy(RBE)/Fx)
	<= 10 cc	15 (Gy(RBE) (3.8 (Gy(RBE)/Fx)

Table 3. Summary of Suggested OAR Dose Constraints for ten-fraction regimens

Esophagus	<= 1 cc	50 Gy (5 Gy/fx)
	<= 10 cc	40 Gy (4 Gy/fx)
Brachial Plexus	Any point	<60 Gy
	<= 1 cc	50 Gy (5 Gy/fx)
	<= 10cc	40 Gy (4 Gy/fx)
Trachea	<= 1 cc	60 Gy (6 Gy/fx)
	<= 10 cc	60 Gy (6 Gy/fx)
Main bronchus and bronchial tree	<= 5 cc	70 Gy (7 Gy/fx)
	<= 10 cc	60 Gy (6 Gy/fx)
Heart	<= 5 cc	70 Gy (7 Gy/fx)
	<= 10 cc	50 Gy (5 Gy/fx)
Whole Lung (Right & Left, subtracting GTV)	V20 GY	<20% (of volume)
	V10 GY	<30%
	V5 GY	<50%
Major vessels	<= 5 cc	70 Gy (7 Gy/fx)
	<= 10 cc	60 Gy (6 Gy/fx)
Skin	<= 1 cc	60 Gy(6 Gy/fx)
Chest wall	<= 10 cc	50 Gy(5 Gy/fx)
Spinal cord*	<=50 cc	50 Gy(5 Gy/fx)
	<= 1 cc	40 Gy(4 Gy/Fx)
	<= 10 cc	30 Gy(2.5 Gy/Fx)

* Spinal cord must be at least 5 mm away from 50 Gy isodose line and maximal dose is less than 42 Gy.

Table 4. Summary of Suggested OAR Dose Constraints for 15-fraction regimens, devised by calculating the biologically equivalent dose (BED) with standard fractionation and then determining equivalent doses for a 15-fraction regimen.

Target	Current Constraint at 2 Gy per fraction to 60-74 Gy	Dose Volume Constraints (BED dose assuming α/β=3 with two fractionation regimens of 2 Gy x 37 fractions and 15 fractions)
Total Lung	V20<40% Mean Lung Dose<20 Gy	V17<40% Mean Lung Dose<17.5 CGE (17.1 Gy)
Liver	40%<50 Gy	40% <40 CGE (38.9 Gy)
Kidneys (both)	1/3<20 Gy	1/3 <18 CGE (17.1 Gy)
Esophagus	20%<70 Gy 50%<50 Gy	20%<55 CGE (52.65 Gy) 50% <40 CGE (38.9 Gy)
Heart	50%<30 Gy 40%<40 Gy	50% <25 Gy (24.6 Gy) 40%<32 Gy (31.9 Gy)
Spinal Cord	Maximum dose 45 Gy	Maximum dose 36 CGE (35.4 Gy)
Brachial Plexus	Maximum dose <60 Gy	<1 cc must receive 50 CGE (45.6 Gy)

4.2.3.3 Critical Structures

All OAR's listed in Table 2-4 should be contoured if there is any risk that the OAR constraints will be exceeded.

4.2.3.4 Primary Site (Primary Lung Lesion, Mediastinal/Hilar/Supraclavicular Disease)

Radiation to the primary site can be delivered with 3D conformal therapy, IMRT, or PBT, at the discretion of the treating radiation oncologist. Standard simulation for treatment to the primary site involves immobilization with an upper body cradle and the arms over the head. The radiation dose to the primary site will be determined by the treating physician and based on normal tissue tolerance and institutional standards. Concurrent chemotherapy is permitted.

In addition, it is acceptable to utilize a simultaneous integrated or sequential boost to further increase dose to the CTV or GTV, at the physician's discretion.

4.2.3.5 Metastatic Sites

Radiation to the metastatic sites can be delivered with 2D/conventional techniques, 3D conformal therapy, IMRT, SRS, or PBT, at the discretion of the treating radiation oncologist. Radiation simulation is dependent on the site being treated, and immobilization devices include but are not limited to upper body cradles, stereotactic body cradles, lower body cradles, SRS immobilization, or a head and neck mass.

The radiation dose to metastatic sites will be determined by the treating physician and based on normal tissue tolerance and institutional standards.

4.2.3.6 Dose Calculation

Doses are to be calculated with CT based heterogeneity corrections, i.e. corrections are made for density differences between air spaces, lungs, water-density, or bone tissue.

5. Symptom Assessment during Protocol Treatment

A) As noted below in "Evaluation of Outcomes of Interest," patients will be evaluated in the clinic for toxicity at follow-up visits every 8 +/- 2 weeks until 1 year, and then less frequently thereafter. Concordant with these clinic visits, the research team will capture toxicities in our toxicity log that meet the following criteria, per institutional policy: a) severe, defined as CTCAE v4.0 Grade 3 or higher, 2) unexpected, or 3) unanticipated. In addition, we will ensure that all relevant toxicities (severe, unexpected, or unanticipated) are documented appropriately in the medical record.

*B) Multiple-symptom assessment tool (**optional**).* Symptoms will be measured by the Lung Cancer module of the MDASI[24]. The MDASI is a multiple-symptom measure of cancer-related symptoms[25] that is sensitive to disease and treatment changes in lung cancer. This instrument is brief, easily understood, and validated in the lung cancer population. Patients rate the intensity of physical, affective, and cognitive symptoms on 0–10 numeric scales, ranging from "not present" to "as bad as you can imagine." Patients also rate the amount of interference with daily activities caused by symptoms on 0–10 numeric scales, ranging from "did not interfere" to "interfered completely." The MDASI-LC has 3 additional items known to be important in assessing patients with MM or MM therapies (constipation, coughing, sore throat). The MDASI-LC takes less than 5 minutes to complete. It can be completed at home using the web or an interactive voice response-computer system that calls the patient to have them rate their symptoms and symptom interference[26]. Symptom severity and interference over time will be a secondary endpoint. The MDASI is included in Appendix C, and this data will be collected from each patient at each follow-up visit as described in the *Evaluation of Outcomes of Interest* section (every 6-8 weeks for the first year).

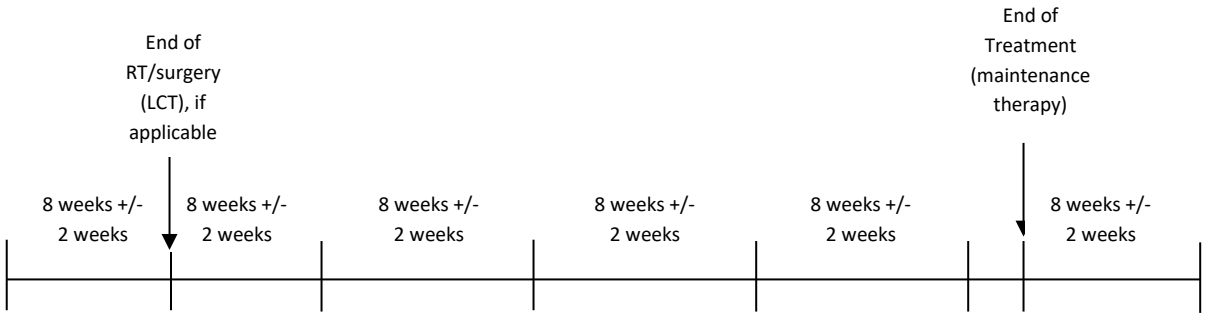
6. Optional Procedures after Induction Chemotherapy

A) Tissue specimen collection for biomarker analysis:
Diagnostic and surgically resected tumor tissue from lung and metastasis sites will be acquired from the source used to establish the diagnosis of malignancy, including archival specimens stored in the Pathology Departments and residual fresh or fixed tissues banked in institutional tissue banks. The tissue samples will include cytology and tissue samples. The samples to be collected will be archival smear slides, cell or tissue blocks, histology sections, and frozen tissue or cell specimens. The cell and tissue samples will be catalogued, review by a pathologist for malignant cell content and pathological analyses, and for correlative molecular marker studies. The molecular marker analysis will include, among others, the analysis of protein expression, gene expression, copy number, mutation, and translocations, and micro-RNA expression abnormalities. The methodology to be used to examine molecular changes will be selected based on the characteristics of the sample collected (e.g., cells or tissue, archival or fresh frozen).

B) Serologies – Blood-based Biomarkers
Optional blood samples will be collected at baseline (e.g., at randomization), then every 8 weeks +/-2 weeks while receiving treatment. If possible, these collections should also be timed to occur at the end of LCT, if applicable, and at the end of chemotherapy cycles 1, 2, and every 2 cycles thereafter. If on the immediate LCT arm, samples will be collected after LCT, then according to the schema above for the delayed/no LCT arm. Blood will be collected and either immediately analyzed or stored frozen until ready for analysis. Cells from blood, including circulating tumor cells (CTCs) will be quantitated and isolated by antibody-based capture methods using tumor antigens including Ep-CAM. Isolated cells will be assessed for markers from relevant pathways through analysis of DNA

(mutations, copy number variations, and single nucleotide polymorphisms (SNPs)), gene expression, and protein. Proteomic studies of circulating proteins including cytokines and angiogenic factors (CAFs) will also be conducted. Additional details of these analyses are provided in Appendix D and Appendix E.

Timeline for Blood Collection



Submit materials as follows:

For central review overnight directly to:
UTMD Anderson Cancer Center,
6767 Bertner Avenue,
Room # T8.3970
Houston, TX -77030
Lab Phone: 713 745 8407

Blood and Tissue banking will be stored at:
CryoGene Lab
9300 Kirby Drive
Suite 200
Houston, Texas 77054

C) Quality of life multiple-symptom assessment pool- see section 5B above.

7. Statistical Considerations

7.1 Preliminaries. The purpose of this study is to test the hypothesis that the treatment paradigm of immediate LCT after induced oligometastatic disease can lead to reduced rates of disease progression. Patients will be randomized between immediate LCT and delayed/no LCT arms. The primary outcome will be progression-free survival (PFS) time, defined as the time from the time of randomization (immediate LCT vs. delayed/no LCT) to disease progression or death. The primary goal will be to compare the PFS times of these two arms.

7.2 Database Used for Collection. Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. [ref] REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information

Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. Following publication study data will be archived in REDCap.

7.3 Randomization. In lieu of stratification, the randomization will balance dynamically on five prognostic covariates related to PFS using the method of Pocock and Simon[27]. The covariates are:

1) number of metastases (1 vs. 2-3), 2) response to first-line chemotherapy (SD vs. PR/CR), 3) CNS metastases (yes/no), 4) N0/N1 vs. N2/N3, and 5) EGFR/EML4ALK status. The randomization will be carried out using the Department of Biostatistics Clinical Trials Conduct Website.

7.4 Design

Design Assumptions:

Primary endpoint	Progression-free survival (PFS)
Null hypothesis	Median PFS equals to 4 months in both groups
Alternative hypothesis	Median PFS equals to 4 months in the delayed/no LCT group and equals to 7 months in the immediate LCT group.
Associated hazard ratio	0.57 = 75% improvement in median PFS
Type I error	10%
Type II error	10%
Accrual rate	2-3 patients/month
Follow-up	9 months

A design with one-sided 10% type I error and 90% power would require an expected number of progression events of 87 under the alternative hypothesis to detect 75% improvement in median PFS. Given these assumptions, this design would require 94 patients *randomized* over 37.6 months with additional 9 months of follow-up. One interim analysis will be performed to allow for the early termination of the trial in light of evidence that the LCT arm is superior to the no LCT arm or there is no difference between the two treatment arms. In order to provide an overall significance level of 0.05 for the study, the interim analysis will use a Lan-DeMets monitoring boundary with an O'Brien-Fleming stopping rule (East 5.4.2.0, Cytel 2011). The interim analysis will be performed when 44 out of the expected 87 events have been observed. Using O'Brien-Fleming test boundaries, the Z-score test cut-off at the interim analysis for stopping and rejecting the null hypothesis will be 2.054, the Z-score test cut-off at the interim analysis for stopping and rejecting the alternative (futility) is -0.203.

In order to obtain 94 patients for randomization, we estimate that 25% of patients (24) will undergo progression of disease during induction chemotherapy based on the first 6 months of patient enrollment. In addition, we anticipate that 20% of patients (19) will refuse randomization after up-front systemic therapy. Therefore, in order to randomize 94 patients, we anticipate that we will need to enroll 94 + 24 + 19 = 137 patients. Note that patients who cross-over to the alternative treatment arm due to toxicity will be censored at the time of crossover, with the last progression-free date being the date of crossover.

7.5 Statistical Analysis Plan

Descriptive statistics will be provided to summarize the patient characteristics and toxicities by the treatment arms (immediate LCT and delayed/no LCT groups). Chi-square test or Fisher's exact test will be applied to compare patient characteristics between the two arms. The balance of the five prognostic covariates (used in the Pocock-Simon's dynamic allocation method) between the two arms will be examined as well. For the primary endpoint, PFS, Kaplan-Meier estimate will be computed, and the log-rank test will be performed to compare the difference of PFS between the two arms. Cox regression model will be applied to correlate PFS with potential covariates in both the univariate and multi-covariate analyses. Patients are considered evaluable for efficacy if they receive at least one of the intended local consolidation therapy. Both the intent-to-treat analysis and analysis among the evaluable patients will be performed. The corresponding results will be compared and contrasted. For the secondary endpoints, similar analysis will be performed on the overall survival and other time-to-event endpoints. Safety and tolerability of the immediate LCT arm and delayed/no LCT arm will be summarized by descriptive statistics. Quality of life will be analyzed by the repeated measures analysis of variance to count for the change before and after treatment and during the follow-up period. Proper transformation will be performed if necessary to transform data to be closer to the Gaussian distribution. All the statistical analyses will be two-sided with a P-value of 0.10 or less considering statistically significant.

Note that the MDACC DSMB will be providing study-wide oversight in regards to the endpoints described above.

To account for patients that crossover for reasons other than RECIST progression of disease (e.g. toxicity, growth of the malignancy that does not constitute RECIST progression), censoring will occur at the time of crossover for our primary analysis. In addition, a secondary time varying covariate Cox model analysis will be done to assess the impact of crossover without RECIST progression.

7.6 Off-study criteria

Patients who enroll on Step 1 will be followed for survival status prior to step 2 if they: 1) progress on chemotherapy, 2) experience toxicity that is deemed to be unacceptable by the treating physician prior to the minimum requirements for induction chemotherapy (i.e. 4 cycles of platinum doublet therapy, 3 months of erlotinib/ afatinib, or 3 months of crizotinib), or 3) refuse randomization. If this occurs, they will remain on study only until proceeding to LCT at the end of induction chemotherapy, if applicable (e.g. without any maintenance therapy or second line systemic therapy), and will be followed for survival status at the conclusion of LCT. Allowing patients to remain on study until the time of LCT will allow for tissue collection if the patient proceeds to surgical resection. Patients who do not proceed with randomization but do not proceed immediately to LCT (receiving maintenance therapy or further systemic therapy) will be followed for survival status immediately after proceeding to maintenance therapy or further systemic therapy.

Patients who continue to step 2, or enroll at step 2, will be followed for survival status at the time of RECIST progression. Patients that are randomized to the immediate LCT arm will be followed for survival status immediately after experiencing RECIST progression. Patients that are randomized to the delayed LCT arm that experience progression will remain on study until the completion of LCT *only if LCT is planned within 6 weeks.* In this scenario, the patient will be followed for survival status at the conclusion of LCT. If no LCT is planned within this timeframe (i.e. if second line chemotherapy is planned and not LCT), the patient will be followed for survival status immediately after experiencing RECIST progression. Allowing patients to remain on study until the time of LCT will allow for tissue collection at that time if the patient proceeds to surgical resection. At that time, crossover can occur between treatment arms, at the treating physician's discretion. Crossover can also occur due to treatment toxicity or an increase in the size of disease that does not meet the criteria of RECIST progression. Patients who do not meet the criteria for RECIST progression and crossover to the alternate arm (e.g., crossover for a reason other than progression) will remain on study and will be followed for survival status.

8. Evaluation of Outcomes of Interest

The primary outcome of this study is PFS. To evaluate this endpoint, radiographic evaluations of the primary and metastatic sites should be conducted at an interval of approximately every 8 weeks after randomization (Step 2) regardless of whether the patient is receiving LCT, maintenance therapy or surveillance, as is standard at our institution (Appendix A). Evaluation will include 1) A PET/CT scan or CT scan of the chest in all patients, and 2) An MRI of the brain or a CT scan of the brain in patients with known brain metastases.

8.1 Reporting Requirements for External AEs

External AEs (EAEs) Requiring Prompt Reporting to IRB

The MD Anderson IRB requires that the investigators submit a prompt report only for external AEs that meet the following criteria for an unanticipated event:

- serious,
- unanticipated,
- related (definitely, probably, or possibly related)

Most of the time, these are events that would require changes in the Investigator Brochure (IB), the informed consent document, or the protocol.
The Sponsor in this situation is responsible for determining if the external AE meets the criteria for prompt reporting to the IRB and the FDA.

Investigators should refer to the 2009 FDA and January 2007 OHRP guidance for reporting of UAEs and UDAEs. Isolated reports should be first reported to the Sponsor in most instances and may not require reporting to the IRB unless the Sponsor ascertains the event to be reportable.

A meaningful analysis or explanation of the reported external event is necessary to enable IRB to make complete determinations in regard to the protection of participants.

Reporting Timeline for prompt reporting:

1. **Within 5 working days from the time the research team becomes aware of the event =** Unanticipated deaths that are attributed by the Sponsor as definitely, probably or possibly

related to study intervention that have occurred within 30 days after the last day of active study intervention.

2. **Within 5 working days from the time the research team becomes aware of the event =** All other serious, unanticipated and definitely, probably or possibly related AEs.

Unanticipated EAEs are required to be reported to the IRB beginning from the date on the MD Anderson IRB letter that approved the protocol.

The MD Anderson IRB does not require the investigators to report EAE that do not meet the criteria for unanticipated events.

The principal investigator (PI) is not required to accept or submit reports to the IRB, that are not compliant with the FDA's final rule or OHRP's reporting policies

9. References

1. Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst 2008;100:1672-94.
2. Reck M, von Pawel J, Nimmermann C, Groth G, Gatzemeier U. [Phase II-trial of tirapazamine in combination with cisplatin and gemcitabine in patients with advanced non-small-cell-lung-cancer (NSCLC)]. Pneumologie 2004;58:845-9.
3. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004;22:330-53.
4. D'Addario G, Felip E. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii39-40.
5. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
6. National Comprehensive Cancer Network guidelines, www.nccn.org. 2011.
7. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
8. 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 2011;12:735-42.
9. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8-10.
10. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol 2011;8:378-82.
11. Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. Clin Cancer Res 2008;14:5255-9.
12. Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: Final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 2011.
13. 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). Radiother Oncol 2006;81:163-7.
14. Hu C, Chang EL, Hassenbusch SJ, 3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 2006;106:1998-2004.
15. Bonnette P, Puyo P, Gabriel C, et al. Surgical management of non-small cell lung cancer with synchronous brain metastases. Chest 2001;119:1469-75.
16. Luketich JD, Martini N, Ginsberg RJ, Rigberg D, Burt ME. Successful treatment of solitary extracranial metastases from non-small cell lung cancer. Ann Thorac Surg 1995;60:1609-11.
17. Stinchcombe TE, Socinski MA. Maintenance therapy in advanced non-small cell lung cancer: current status and future implications. J Thorac Oncol 2011;6:174-82.
18. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:591-8.
19. Perol MC, B.; Milleron, J.; Gervais, R.; Barlesi, F.; Westeel, V.; Crequit, J.; Lena, A.; Vergnenegre, D.; Perol, D. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatmetn after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. J Clin Oncol 2010;28:Abstract 7507.
20. L. G. Paz-Ares FDM, M. Dediu, M. Thomas, J. Pujol, P. Bidoli, O. Molinier, T. P. Sahoo, E. Laack, M. Reck, J. Corral, S. A. Melemed, W. J. John, N. Chouaki, A. Zimmerman, C. M. Visseren Grul, C. Gridelli. PARAMOUNT: Phase III study of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care immediatly following induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer. J Clin Oncol 2011;29.
21. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-40.

22. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-9.
23. Kabbinavar FM, VA; Johnson, BE; O'Connor, PG; Soh, C. Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). . Program and abstracts of the 2010 Annual Meeting of the American Society for Clinical Oncology 2010:Abstract 7526.
24. Mendoza TR, Wang XS, Lu C, et al. Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson Symptom Inventory. Oncologist 2011;16:217-27.
25. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634-46.
26. Cleeland CS, Wang XS, Shi Q, et al. Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. J Clin Oncol;29:994-1000.
27. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.
28. Byers LA, Holsinger FC, Kies MS, et al. Serum signature of hypoxia-regulated factors is associated with progression after induction therapy in head and neck squamous cell cancer. Mol Cancer Ther 2010;9:1755-63.
29. Kopetz S, Hoff PM, Morris JS, et al. Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. J Clin Oncol 2010;28:453-9.
30. Hanrahan EO, Lin HY, Kim ES, et al. Distinct patterns of cytokine and angiogenic factor modulation and markers of benefit for vandetanib and/or chemotherapy in patients with non-small-cell lung cancer. J Clin Oncol 2010;28:193-201.
31. Hanrahan EO, Ryan AJ, Mann H, et al. Baseline vascular endothelial growth factor concentration as a potential predictive marker of benefit from vandetanib in non-small cell lung cancer. Clin Cancer Res 2009;15:3600-9.
32. Nikolinakos PG, Altorki N, Yankelevitz D, et al. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor shrinkage in early-stage non-small cell lung cancer patients treated with pazopanib. Cancer Res 2010;70:2171-9.
33. Schneider BP, Wang M, Radovich M, et al. Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. J Clin Oncol 2008;26:4672-8.

Appendix A. Timeline of evaluations before, during and after randomization.

Study Test	Baseline (prior to randomization)	After randomization, prior to treatment – Treatment= 0 weeks	8 weeks +/- 2 weeks	16 weeks +/- 2 weeks	24 weeks +/- 2 weeks	32 weeks +/- 2 weeks	40 weeks +/- 2 weeks	48 weeks +/- 2 weeks
PET/CT or CT Scan Chest	X (PET/CT scan preferred)		X	X	X	X	X	X
MRI Brain or CT Head	X (all patients, MRI Brain preferred)		X (if brain mets)	X (if brain mets)	X (if brain mets)	X (if brain mets)	X (if brain mets)	X (if brain mets)
Blood-Based Biomarkers (optional study)		X	X	X	X	X	X	X
Toxicity Assessment		X	X	X	X	X	X	X
Quality of Life Symptom Assessment (optional study)		X	X	X	X	X	X	X

Appendix B. MD Anderson Symptom Inventory (MDASI)

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

M. D. Anderson Symptom Inventory - Lung Cancer (MDASI-LC)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please rate each of these symptoms from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be).

CORE Items	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

MDASI-LC - December, 2010

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

Lung Cancer - Specific Items	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **coughing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **sore throat** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items **in the last 24 hours**:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
17. General **activity**?	○	○	○	○	○	○	○	○	○	○	○
18. **Mood**?	○	○	○	○	○	○	○	○	○	○	○
19. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
20. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
21. **Walking**?	○	○	○	○	○	○	○	○	○	○	○
22. **Enjoyment** of life?	○	○	○	○	○	○	○	○	○	○	○

MDASI-LC - December, 2010

Appendix C. Biomarker analyses

Circulating Tumor Cells (CTCs)

Isolation of CTCs and molecular analysis of these CTCs including mutational profiling.

We will be isolating CTCs using methods such as the CTC microfluidic chip previously described (N Engl J Med 2008; 359:366-377). Other methodologies that are not dependent on antibody are also being tested and will be used if their utility and technical performance has been established. The captured cells of interest can be subsequently interrogated through immunohistochemistry (e.g. fluorescent in situ hybridization or FISH) somatic mutation profiling (e.g. Sequenome profiling), SNP profiling, and gene expression analysis with a focus on pathways relevant to NSCLC and drugs under investigation (e.g. EGFR, MEK, PI3K pathways).

Previously we have established that rare circulating cells can be quantitated using frozen peripheral blood mononuclear cells (PBMCs) (Clin Canc Res 2007; 13(9): 2643-50). This permits batched analysis of stored samples. Therefore, we will isolate and freeze PBMCs using methods we have previously described. From each sample, blood will be subjected to gradient separation of mononuclear cells, placed in DMSO-containing freeze media, cooled using a controlled freeze protocol, and stored at -80C until analysis as described above.

Cytokines and Angiogenic Factors (CAFs)

CAF profiling using serum or plasma to detect biomarkers and signatures of response

The availability of multiplexing technologies permits the simultaneous assessment of large numbers of biologically relevant proteins, such as cytokines, angiogenic factors, and receptors, and soluble markers of hypoxia and endothelial damage, using small amounts (i.e., less than one milliliter) of plasma. We refer to the broad assessment of these multiple markers as the CAF (cytokine and angiogenic factor) profile. We and other investigators have studied a number of these circulating biomarkers in peripheral blood and observed that baseline levels , or changes in these factors, may be markers of drug response or the emergence of therapeutic resistance [28-32].

Circulating CAFs will be assessed using established methods as we have previously described [28-32]. A CAF profile (typically 60-70 analytes) of plasma biomarkers will be assessed using a combination of multiplex technology (e.g. Luminex and Searchlight platforms) and enzyme-linked immunosorbent assays (ELISA). Multiplex magnetic bead-based technology enables the simultaneous quantitation of up to 100 analytes. These Luminex based assays contain dyed beads conjugated with monoclonal antibodies specific for a target protein. The antibody-conjugated beads are allowed to react with sample and a secondary, or detection, antibody in a microplate well to form a capture sandwich immunoassay. Multiplex assays can be created by mixing bead sets with different conjugated antibodies to simultaneously test for many analytes in a single sample. The use of this technique has been well documented in the literature and results are comparable to that of ELISA (8-10). Currently up to 50 human cytokines can be analyzed from 3 separate kits using a total volume of less than 1 milliliter. The remainder of analytes will be determined using by validated, enzyme-linked immunosorbent assays (ELISA) assays such as Human Osteopontin (OPN), CA-9, Collagen IV, sVEGFR2, NGAL; and using the Searchlite multiplex platform. Other analytical platforms will be considered if they are established to have advantages (e.g. lower volume requirements or greater sensitivity). For each plate, the standard curves will be assessed to ensure that the expected assay range was achieved. For each individual sample, the mean concentration is calculated for duplicate samples, and the coefficient of variance % (CV%) is calculated for each of the analytes. If the median CV% is greater than 25%, analysis of the sample was repeated. In our experience, less than 10% of samples require repeat analysis.

Single Nucleotide Polymorphism Analysis. Prior studies have established that germline SNPs in cancer related pathways (e.g. VEGF, VEGFR2) may be markers for therapeutic response [33]. To identify new markers for the treatments in this study we will investigate germline SNPs relevant to the treatment regimens in this study. SNPs will be selected based on several criteria including: previous report of an association with an inflammatory disorder, angiogenesis, lung cancer, or another cancer; minor allele frequency (prioritizing those with frequency of at least 5%); location in the promoter, untranslated region (UTR), or coding region of the gene. The SNPs will be genotyped using standard methods such as SNPlex, a technology developed by Applied Biosystems that enables simultaneous genotyping of up to 48 SNPs in a single tube using an oligonucleotide ligation assay. The assay principle and procedures are detailed in the manufacturer's user guide (PN4360858). As methods for assessing SNPs are rapidly improving we will evaluate and potentially incorporate other available methods for SNP assessment at the time of analysis.

Appendix D. Blood-based biomarkers: collection, processing, and storage of plasma, serum, and peripheral blood mononuclear cells (PMBCs).

I. **Whole Blood for CTCs**

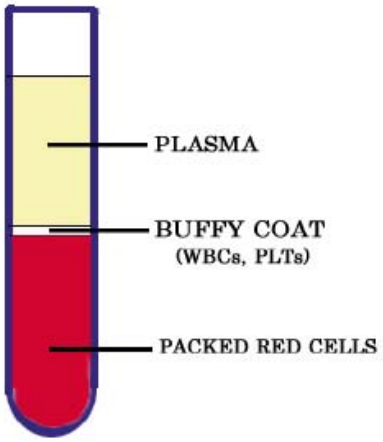
1. Collect a total of 3purple top (EDTA) tubes for analysis of blood-based biomarkers.

II. **Preparation of Plasma:**

1. Label three (3) 1 ml cryovials with the study number, case number, and procedure date, and clearly mark cryovials "plasma."
2. Collect 10 mL of blood into an EDTA Vaccutainer® (purple top)
3. Process: Spin EDTA (purple top) tube in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
4. **Centrifuge within 30 minutes of collection.** If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
5. Aliquot plasma into the 1 ml cryovials labeled with the study and case numbers and procedure date and marked "plasma."
6. Place cryovials into biohazard bag.
7. Use study labels* to label bag.
8. Store at a minimum –70 Celsius until ready to analyze.
9. Place all cryovials into corrugated boxes.
10. Use study labels* to boxes.
11. Store at a minimum –70 Celsius until ready to analyze.

III. **Preparation of Buffy coat:**

For a visual explanation of Buffy coat, please refer to diagram below.



1. Label three (3) 1 ml cryovials with the study number, case number, and procedure date, and clearly mark cryovials "buffy coat."
2. Process: Spin EDTA (purple top) tube in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
   Centrifuge within 30 minutes of collection.
   If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Remove plasma close to the buffy coat and keep the plasma for procedure II (*see above instructions for plasma collection*)
4. Remove the buffy coat cells carefully and place into the 1 ml cryovials labeled "buffy coat"

(*it is acceptable for a few packed red cells inadvertently to be collected in the process*).

5. Place equal volume of cell-storage solution (RPMI/DMSO (70:30))
6. Store buffy coat cryovial at -70 C until analyzed.