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Maintenance Chemotherapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) plus Maintenance Chemotherapy for Stage IV Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II Trial

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Signature Page

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

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PROTOCOL SYNOPSIS

Summary

This protocol is a randomized phase II trial of maintenance chemotherapy versus consolidative Stereotactic Body Radiation Therapy (SBRT) plus maintenance chemotherapy for patients with Stage IV non-small cell lung cancer (NSCLC). The core hypothesis to be tested is that the use of consolidative SBRT followed by maintenance chemotherapy in patients with less than or equal to 6 metastatic sites (primary + 5) will improve progression free survival (PFS) compared to maintenance chemotherapy alone.

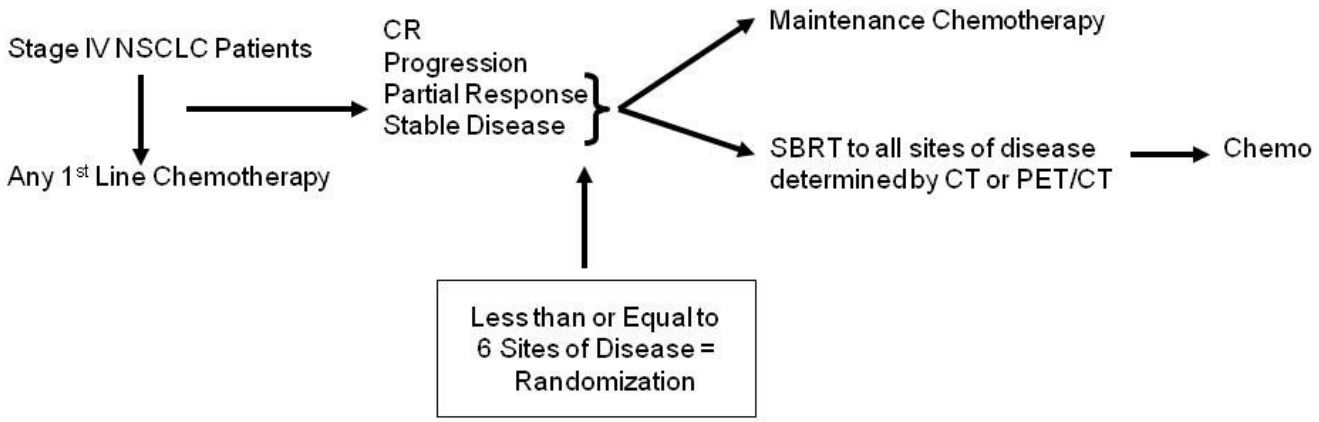
Prior to accrual on the trial, patients with Stage IV NSCLC will be treated with standard first-line chemotherapy. Patients who achieve a partial response or stable disease by imaging criteria with fewer than or equal to six sites of oligometastatic disease will be randomized to maintenance chemotherapy or consolidative SBRT to all sites of disease (followed by maintenance chemotherapy at the medical oncologist's discretion). Choices of first line and maintenance chemotherapy will be determined by the medical oncologist based on clinical appropriateness. Preliminary data from an earlier phase II single arm study with SBRT plus Tarceva demonstrated significant PFS and OS with limited toxicity in patients with limited metastatic stage IV NSCLC who progressed through first line platinum doublet chemotherapy when compared to historical findings (unpublished data). The goal of the former study was to validate the potential role of cytoreduction in promoting progression free survival.

The primary endpoint of the current proposed study is progression free survival. The estimated progression free survival is 5 months for patients treated with maintenance chemotherapy alone based on historical data from randomized phase III trials. We anticipate an improvement of progression free survival to 10 months with the addition of SBRT in patients with stable or partial response to first line therapy with oligometastatic disease. This estimate of improved progression free survival is in part based on our prior phase II protocol for patients with Stage IV NSCLC with progression of disease on first line therapy treated with SBRT and Erlotinib. Progression free survival in that study was 10.7 months. Our estimates are also based on the experiences of several studies that have examined radiation in consolidative fashion to systemic therapy for oligometastatic disease.

A two-sided log-rank test with an overall sample size of 36 patients (18 patients in the maintenance chemotherapy arm and 18 patients in the SBRT arm) achieves 80% power at a 10% significance level to detect a hazard ratio of 0.4000 when the median progression-free survival (PFS) times are 4 and 10 months in the maintenance group and SBRT treated group, respectively. Patients will be accrued within 24 months with a follow-up period of 12 months after the end of the accrual period.

Schema

Randomized Phase II Trial Comparing Maintenance Chemotherapy vs Consolidative SBRT for Stage IV NSCLC Patients with Oligometastatic Disease



Patient off study – When progression by imaging cannot be adequately addressed by SBRT (either from too many sites of disease progression or failures within previously treated sites with SBRT)

Primary End Point – PFS
Secondary End Points – OS, Toxicity, Biologic Correlates, Cost-Benefit Analysis, QoL

Longitudinal Biologic Correlates – Could include CTCs, Cytokines, Growth factors, Biopsy of Recurrences and evaluation of SNPs, Deep Sequencing, etc.

1. INTRODUCTION

Lung cancer is a leading cause of cancer-related mortality. An estimated 228,190 new cases of lung cancer are expected in 2013 in the United States with an estimate of approximately 160,000 deaths [1]. While advances in local and systemic therapy have been achieved in recent years, there remains a great need for improvement in clinical management. Approximately two-thirds of patients present with advanced stage non-small cell lung cancer (NSCLC) and often are treated with chemotherapy alone [2]. It remains a poorly controlled and fatal disease, with estimates of median survival of 11 months following first line chemotherapy with a platinum doublet [3].

The principle of oligometastases was well popularized in 1995 by Hellman and Weichselbaum who hypothesized that metastastic disease occurs in a step-wise manner, initially with limited metastases followed by progression to widespread disease. Early on, metastases may be limited in number and location based on interaction of tumor cells with target organs in a "seed and soil" pattern [4,5]. With improvements in imaging, including PET/CT and MRI, identification of isolated metastatic deposits is accomplished with higher sensitivity and specificity than ever before. A significantly greater proportion of patients may be identified early in the metastatic spectrum and offered potentially curative local treatment, creating a new paradigm in the management of limited volume metastatic NSCLC. The traditional grouping of all patients with metastatic disease may no longer be relevant with potential implications in changing of tumor staging.

Support for the benefit provided by treatment of oligometastases was first derived from surgical metastectomy. Patients treated with surgical resection of hepatic, pulmonary, or adrenal metastases have had improved rates of survival with resection [6-8]. Furthermore, advancements in systemic therapy may convert a greater proportion of patients with widely metastatic disease to a limited volume metastatic state. With current first line platinum doublet chemotherapy, up to 70-80% of patients achieve either a partial response or stable disease [9]. In those patients who do show progression of disease, up to 65% progress only at sites present prior to the start of first line chemotherapy [10]. This represents a large cohort of patients who may be candidates for early treatment of oligometastatic disease.

Systemic maintenance therapy with targeted and cytotoxic agents has now shown statistically significant benefits in both progression free and overall survival. By intervening with non-invasive locally ablative stereotactic therapy prior to maintenance chemotherapy there is the potential for further benefits in PFS and/or OS. Stereotactic radiotherapy has the advantage over surgical metastectomy in that there is minimal toxicity with quicker recovery and limited delay in initiation of maintenance chemotherapy.

1.1 Maintenance Chemotherapy for Non-Small Cell Lung Cancer

The introduction of maintenance chemotherapy has led to statistically significant, albeit modest, gains in progression free survival and overall survival following standard first line platinum doublet chemotherapy (Table 1). Drugs used for maintenance chemotherapy can be considered either cytotoxic or biologic and include Docetaxel, Pemetrexed, Erlotinib, Gefitinib, Gemcitabine, and Bevacizumab. Maintenance chemotherapy can be given as continuation maintenance, utilizing one or more first line drugs, or as switch maintenance, utilizing a previously unused

drug. A recent meta-analysis has proven the benefit of switch maintenance over continuation maintenance in both overall survival and progression free survival in the stage IV NSCLC population [11]. Unfortunately, these drugs alone provide modest gains and oblige patients to indefinite chemotherapy with their associated toxicities.

Table 1.

Study/Author	Drug	PFS (months)	OS (months)
Ciuleanu et al	Pemetrexed	4.3 vs 2.6*	13.4 vs 10.6*
PARAMOUNT	Pemetrexed	4.1 vs 2.8*	13.9 vs 11.0*
Capuzzo et al	Erlotinib	2.8 vs 2.6*	12 vs 11*
Brodowicz et al	Gemcitabine	3.6 vs 2.0*	13 vs 11
EORTC 08021	Gefitinib	4.1 vs 2.9*	10.9 vs 9.4
Fidias et al	Docetaxel	5.7 vs 2.7*	12.3 vs 9.7
INFORM	Gefitinib	4.8 vs 2.6*	18.7 vs 16.9
AVAPERL	Pemetrexed + Bevacizumb vs Pemetrexed	7.4 vs 3.7*	Pending

** Statistically significant (p <0.05)*

1.2 Rationale for Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) is an emerging treatment paradigm defined in the American Society of Therapeutic Radiology and Oncology guidelines as a “treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body” [12].

SBRT allows the delivery of ablative treatment doses using highly conformal radiotherapy to an increasing number of sites in the body. By providing treatment as a short course of therapy, patients are not subjected to prolonged treatment times that may compromise quality of life. Treatment is delivered non-invasively and with an increasing body of data supporting its tolerability with limited toxicity.

To date, there have been no successful, prospective randomized studies which examine the role of locally aggressive therapy in limited volume stage IV NSCLC. The NCCTG initiated a randomized phase III trial in patients with stage IV NSCLC, treating 1 to 3 sites of metastatic disease following 4-6 cycles of systemic therapy. Stereotactic body radiotherapy was not used. Patients were treated with traditional fractionation to 60 Gy in 30 fractions or 45 Gy in 15 fractions. Unfortunately, this study closed due to poor accrual [13]. A second study from the University of Chicago randomized patients with oligometastatic NSCLC to SBRT during the third and fourth cycle of docetaxel/cisplatin first line chemotherapy. Unfortunately, this study also had difficulty with accrual and closed early [14]. Currently, a single arm phase II trial at Wake Forest

University is the only SBRT study open and accruing patients with limited volume stage IV NSCLC [15].

Preliminary data from our earlier phase II single arm study demonstrated statistically significant improvements in both PFS and OS in patients with Stage IV NSCLC treated with SBRT plus Tarceva. The patient population chosen in this study was unique, with treatment limited to patients who progressed through first line platinum doublet chemotherapy and with limited metastases. Historically, the outcomes in this population are extremely poor. Nonetheless, in this study progression free survival was 10.7 months with median overall survival of 20.8 months. Furthermore, in patients tested for the EGFR mutation, 0/10 patients were positive. It is known that the benefit of Tarceva is most significant in patients who possess the EGFR mutation which lends support to the notion that locally ablative radiotherapy proves effective in improving progression free and overall survival [16].

Retrospective data from the University of Chicago is available for patients with oligometastatic NSCLC treated with SBRT to 1 to 5 sites of metastatic or primary disease following systemic therapy. Patients were treated to all known sites of active disease at a minimum of two weeks following first line systemic therapy. The most commonly used fractionation schedule was 50 Gy in 10 fractions. A total of 62 lesions were treated in 25 patients with a median of 2 lesions treated per patient. The median lesion size was 2.65 cm. Treatment was well tolerated with only 2 patients suffering Grade 3 toxicity. With a median follow-up of 14 months, the median PFS was 7.6 months and median OS was 22.7 months. Progressive disease was identified in 52% of patients following initial first-line chemotherapy. Analysis of PFS and OS in patients with progressive versus stable/regressive disease following first line chemotherapy showed the former population to possess significantly worse PFS and OS relative to the latter. Despite the significant number of patients with progressive disease the results of this study show a PFS that is higher than those achieved by maintenance chemotherapy alone [17].

Further support for selection of patients with stable or partial response to first-line chemotherapy is available from the University of Rochester. Patients with up to five sites of oligometastatic disease of any histology were treated to all sites of disease with SBRT. There were 121 patients enrolled prospectively with 74% treated to 50 Gy in 5 fractions. Patients who achieved a response or stable disease to initial systemic therapy prior to SBRT showed significantly higher rates of overall survival and freedom from distant metastases compared to those with progressive disease following initial systemic therapy [18].

A retrospective review of patients treated at the University of Rochester compared outcomes of patients with stage III NSCLC treated with curative intent radiotherapy against patients with limited volume stage IV NSCLC who received SBRT. Oligometastases was expanded in this review to fewer than 8 sites of disease. Patients with stage III NSCLC were treated to an average dose of 60 Gy via a 3-D conformal technique with or without chemotherapy. Patients with limited volume metastases were treated with SBRT to a dose of 50-60 Gy in 5-10 fractions. Patients with limited volume stage IV NSCLC treated with SBRT had higher rates of 5-year survival relative to patients with stage III NSCLC treated definitively, 14% vs 7%, respectively. The 5-year survival data for Stage III patients was lower than expected in this study, however, the survival of patients with limited volume stage IV NSCLC is comparable to historical data of patients with stage III NSCLC treated definitively [19].

The most commonly treated sites of metastatic disease with SBRT are sites within the lung and liver. A recent multi-institutional Phase I/II trial from the University of Colorado enrolled patients with 1-3 pulmonary metastases from a solid tumor, cumulative tumor diameter < 7 cm, and adequate pulmonary function (FEV1 > 1.0 L, DLCO > 40%). The planning target volume (PTV) was constructed from the gross tumor volume (GTV) by expanding 5 mm radially and 10 mm craniocaudally, and 7 mm radially and 15 mm craniocaudally, when using active breathing control and abdominal compression, respectively. In the initial phase, the SBRT dose was escalated from 48 Gy to 60 Gy in 3 fractions. The percent of normal lung receiving more than 15 Gy (V15) was restricted to less than 35%. Dose-limiting toxicities (DLT) included acute grade 3 lung or esophageal toxicity or any acute grade 4 toxicity. Thirty- eight patients were enrolled on the study, 9 patients in the Phase I portion and 29 on Phase II, receiving 60 Gy in 3 fractions, for a total of 63 lesions treated. With a median follow-up of 15.4 months, the actuarial in-field local control at 2 years was 96% with a median overall survival of 19 months. Treatment was well tolerated with only 7.9% of the population suffering grade 3 toxicity with no grade 4 or 5 toxicity [20].

A second multi-institutional Phase I/II trial from the University of Colorado enrolled patients with 1-3 liver metastases from any solid tumor, cumulative maximum tumor diameter < 6 cm, adequate liver and kidney function, and no chemotherapy 14 days before or after SBRT. In the phase I portion the SBRT dose was escalated from 36 Gy to 60 Gy in 3 fractions. Thirteen patients were treated with a dose of less than 60 Gy and 36 patients treated at 60 Gy, for a total of 63 hepatic lesions. Volume delineation was similar to that in the lung oligometastases trial, with the PTV defined as as GTV expanded by 5 mm radially and 10 mm craniocaudally, and 7 mm radially and 15 mm craniocaudally, with active breathing control and abdominal compression, respectively. At least 700 cc of normal liver had to receive a total dose <15 Gy and the sum of the left and right kidney volume receiving 15 Gy had to be less than 35%. With a median follow-up of 16 months the 2 year actuarial in-field local control was 92% with a median overall survival of 20.5 months. Treatment was well tolerated with 1 patient suffering Grade 3 soft-tissue toxicity, no grade 4 or 5 toxicity, and no instances of radiation induced liver dysfunction (RILD) [21].

A recent prospective dose escalation study at the University of Chicago enrolled patients with 1 to 5 oligometastases of any histology to receive SBRT to any site amenable to treatment. The starting dose was 24 Gy in 3 fractions. Treatment dose was escalated at 2 Gy per fraction intervals with a ceiling of 60 Gy in 3 fractions. A total of 61 patients were evaluated with 113 treated sites. The final dose cohort with sufficient follow-up and enrollment was 42 Gy. With a median follow-up of 20.9 months, the median PFS was 5.1 months. Patients with 1 to 3 metastases were found to have significantly longer PFS than patients with 4 to 5 metastases. It is significant to note in this study that 55% of patients had a limited pattern of progression in 3 or fewer sites, which may have been amenable to further SBRT [22].

1.3 EGFR Mutation/ ALK-Positive Mutation

Activating mutations in EGFR, which occur with exon 19 deletions or exon 21 point mutations, have been identified in up to 26% of patients with non-small cell lung cancer, most commonly in patients of Asian descent [23]. EGFR tyrosine kinase inhibitors with proven efficacy include gefitinib and erlotinib. Four prospective randomized trials in the Asian population and one randomized trial in the European population have evaluated first-line treatment with gefitinib or

erlotinib in EGFR-mutant NSCLC. All five trials have shown a significantly improved rate of progression free survival in patients compared to chemotherapy [24-28].

Anaplastic lymphoma kinase is aberrantly activated in approximately 4% of NSCLC, due to chromosomal rearrangement leading to the oncogenic fusion kinase EML4-ALK. These patients present with young age of onset, minimal or absent smoking history, and adenocarcinoma histology. Crizotinib is an orally available small-molecule inhibitor of ALK and c-Met receptor tyrosine kinase currently in clinical trials. No randomized prospective data yet exists for targeting with crizotinib. However, a prospective phase I clinical trial has now shown a 61% objective response with median progression free survival of 10 months in ALK positive patients with Stage III-IV NSCLC [29].

1.4 Study Rationale

SBRT is a rapidly disseminating practice that may be performed with a wide range of dedicated equipment. It is currently under active clinical investigation at numerous institutions worldwide. The utilization of maintenance chemotherapy alone following first line chemotherapy including novel biologic or cytotoxic agents is now proven to provide modest benefits in progression free survival and overall survival. SBRT prior to any potential maintenance chemotherapy may provide further benefit over maintenance chemotherapy alone with respect to PFS.

SBRT has an acceptable toxicity profile with an increasing number of sites in the body amenable to treatment. It has the added benefit of providing a full course of treatment within a few fractions, providing an alternative to a protracted course of therapy with a non-invasive technique. By eradicating gross disease it is believed that progression free survival will be improved compared to maintenance chemotherapy.

For patients with oligometastatic disease, there exists limited effective treatment beyond second line chemotherapy. By expanding the available treatment options with SBRT while preventing progression and potentially prolonging survival, this study will prove practice changing. Furthermore, it is anticipated that short course radiotherapy will not compromise the patient's quality of life. We hope to show that the ease of delivery of short course ablative radiotherapy will increase the percentage of patients with stage IV NSCLC who receive consolidative therapy following first line chemotherapy.

1.5 Study Design

This study is a two-arm randomized phase II trial. All patients enrolled on the trial will have received 4-6 cycles of first line chemotherapy. Patients with non-squamous histology may have the addition of bevacizumab to first-line therapy at the medical oncologist's discretion. Patients receiving first-line erlotinib, crizotinib for EGFR mutant-positive or EML4-ALK positive NSCLC will be excluded. Patients will be assessed within 42 days following completion of first line chemotherapy with repeat diagnostic CT or PET/CT. Patients with stable disease or partial response with oligometastatic disease, defined by six or fewer sites amenable to SBRT, will be randomized within 21 days of imaging to either maintenance chemotherapy alone or SBRT to all gross disease followed by maintenance chemotherapy. SBRT will be given according to

guidelines outlined in Section 4. Maintenance chemotherapy will continue until disease progression, intolerable toxicity, or death.

Patients who develop new lesions amenable to SBRT during follow-up imaging and not previously treated will be evaluated for additional SBRT at the Radiation Oncologist's discretion. This event will not constitute progression if the lesion is treated by SBRT. However, if the lesion is not amenable to SBRT, the patient is either unwilling to pursue further treatment or cannot tolerate treatment due to coexisting comorbidities, then progression will be deemed to have occurred.

SBRT, in and of itself, can alter the effectiveness of imaging in determining progression vs. response. Imaging at 3 months post SBRT will be instituted as a standard on the trial but will mostly relate to disease outside the irradiated fields. Imaging at other times may be instituted earlier based on clinical need. Because the sites of initial gross disease may still be obfuscated by the SBRT at the time of the 3 month assessment, caution will be observed in interpreting any lack of evidence of progression relative to non-SBRT treated historical controls.

2. OBJECTIVES

2.1 Primary

The primary objective of this study is to evaluate the effect of SBRT with or without maintenance chemotherapy versus maintenance chemotherapy alone on progression free survival

2.2 Secondary

Secondary objectives include the following:
1. To describe the actuarial rate in-field local control and rate of out-of-field disease progression.
2. To evaluate the safety of SBRT with metastatic NSCLC after prior chemotherapy
3. To evaluate overall survival after SBRT followed by maintenance chemotherapy in comparison to maintenance chemotherapy alone.
4. To evaluate the duration of maintenance chemotherapy and time to initiation of third line systemic agent (chemotherapy or biologic agent)

3. TRIAL POPULATION

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Patients must have biopsy proven metastatic NSCLC (Stage IV).
2. Patients must have received first line chemotherapy, from 4-6 cycles, and achieved stable disease or a partial response.
3. Patients receiving first-line erlotinib, crizotinib for EGFR mutant-positive or EML4-ALK positive NSCLC will be excluded.
4. Age ≥ 18 years
5. Patients must have measurable disease at baseline.
6. Patients can have up to only 6 discrete active extracranial lesions (≤3 in the liver and ≤3 in the lung) identified by diagnostic CT or PET/CT scan or MRI within 8 weeks prior to the initiation of SBRT.

a) For patients who have received prior radiotherapy to the primary site in the lung, residual PET activity is difficult to interpret and will not be considered a site of active disease if the CT appearance is stable or improved over an interval of at least three months
b) Patients who previously received radiotherapy to the primary site will be ineligible if there is CT evidence of disease progression within the past 3 months.
c) Patients with previously un-irradiated primary sites will be potentially eligible, but special considerations apply (section 4.3.2).
d) Up to 2 contiguous vertebral metastases will be considered a single site of disease.

7. Patients must have a KPS >60
8. AST, ALT & Alkaline phosphates must be ≤ 2.5X the upper limit of normal. Total bilirubin must be within the limit of normal.
9. Patients should have adequate bone marrow function as defined by peripheral granulocyte count of ≥1500/mm³.
10. Patients should have adequate renal function (serum creatinine ≤1.5 times the ULN).
11. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

    11.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

    - Has not undergone a hysterectomy or bilateral oophorectomy; or
    - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).
12. Patients who would be receiving SBRT for lung tumors who are known or suspected by the treating radiation oncologist to have compromised lung function must have a documented forced expiratory volume in 1 second (FEV1) ≥ 1L.
13. Patients must provide verbal and written informed consent to participate in the study.

3.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not to be enrolled in this study.

1. Patients who previously received radiotherapy to the primary site with CT evidence of disease progression at the primary site within 3 months following the initial radiotherapy.
2. Patients with untreated brain metastases Patients with serious, uncontrolled, concurrent infection(s).
3. Significant weight loss (>10%) in the prior 3 months.
4. Because the tolerance dose of SBRT to the gastrointestinal tract is not established, patients with metastatic disease invading the esophagus, stomach, intestines, or mesenteric lymph nodes will not be eligible.
5. Patients with cutaneous metastasis of NSCLC.
6. Patients with more than 6 discrete extra-cranial lesions.
7. Participation in any investigational drug study within 4 weeks preceding the start of study treatment.

8. Unwillingness to participate or inability to comply with the protocol for the duration of the study.
9. Patients who are pregnant. Patients with reproductive capability will need to use adequate contraception during the time of participation in the study.

4. SBRT DOSE AND TECHNIQUES

SBRT will begin within 3 weeks after randomization to the SBRT arm.

Stereotactic treatment is the targeting, planning, and directing of treatment fields guided to a target based on known 3-D coordinates related to reliable fiducial markers. This differs from conventional radiation therapy in which treatment is guided by skin or bony landmarks assumed to correlate to the target volume based on the initial simulation. Stereotactic Body Radiation Therapy (SBRT) in this study will be delivered with an ablative range of dose per fraction. Treatment will account for inter/intra-fractional errors with careful dosimetry that delivers an ablative dose to the metastatic lesion(s) while respecting normal tissue constraints.

4.1 SBRT Prescription

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

Prescription Dose

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

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

If the radiation oncology physician believes that the fractionation schemes listed above for any lesion (primarily bulky mediastinal/hilar disease) is not achievable with normal tissue constraints, they can treat that site to 45 Gy in 15 fractions. This decision will be discussed with the PI of the study. Each treatment may be given once a day for 3 weeks excluding weekends/holidays, using standard tissue constraints and PTV coverages for traditional IMRT techniques.

4.2 Planning Constraints and Concerns

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

Cutaneous metastases are an uncommon manifestation of non-small cell lung cancer that are typically associated with poor prognosis [12-14]. Patients with cutaneous metastases will be

ineligible. As this may represent a group of patients with particularly poor prognosis, again this will be considered within any comparison with historical controls.

It is well established that for palliative effect for a painful bone metastasis, a single dose of 8 Gy is usually as effective as 30 Gy [15]. Long term survival after bone metastasectomy has been reported [17]. Irradiation of non-spinal skeletal sites does not generally require specialized techniques of treatment. Metastases in major lower extremity weight-bearing bones should undergo surgical stabilization if there is plain film evidence of cortical erosion.

Corticosteroid premedication will not be mandated, although it can be used at the discretion of the treating oncologist (in which case, its use needs to be reported). Analgesic premedication to avoid general discomfort during long treatment durations is recommended when appropriate.

4.3 Technical Factors

4.3.1 Physical Factors

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

4.3.2 Dose Verification at Treatment

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

4.3.3 Treatment Platforms

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

4.4 Simulation/Image Guidance

4.4.1 Patient Positioning

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

At the time of simulation for patients who will receive SBRT to the lung and/or liver, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a

respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required.

4.4.2 Image Guidance

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

4.5 Treatment Planning/Target volumes

4.5.1 Image Acquisition

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

4.5.2 Target Volumes

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

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

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

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

4.6 Dosimetry

4.6.1 3D-Conformal Planning

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

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

4.6.2 Intensity Modulated Radiation Therapy (IMRT)

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

4.6.3 Dose Calculations

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

Successful treatment planning will require accomplishment of all of the following criteria:

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

4.7 Normal Tissue Dose Constraints

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

The possibility that SBRT-induced fibrosis might cause occlusion of large central airways, thus impeding ventilation distal to the occlusion has been well considered. [22] An adjustment to the fractionation scheme may be made if, in the opinion of the treating radiation oncologist, the following conditions apply: (1) the location of a lung lesion is close enough to a large proximal bronchial airway such that occlusion might occur, and (2) compromised ventilation to the segment(s) of lung potentially affected would cause clinically significant adverse consequences.

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

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

One Fraction

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

Parallel Tissue	Critical Volume (cc)	Critical Volume Dose Max (Gy)		Endpoint (≥Grade 3)
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.6 Gy	V-8Gy <37%	Pneumonitis
Liver	700 cc	11 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	9.5 Gy		Basic renal function

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

Three Fractions

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

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

Five Fractions

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Spinal Cord and medulla	<0.35 cc <1.2 cc	22 Gy 15.6 Gy	28 Gy	myelitis

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

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

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

4.8 Radiation Therapy Quality Assurance

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

5. STUDY MEDICATIONS

Currently accepted drugs used for maintenance chemotherapy include Erlotinib, Pemetrexed, Docetaxel, Gemcitabine, and Bevacizumab. These drugs are standard of care and are commercially available.

5.1 **Erlotinib** (Tarceva®)

5.1.1 Formulation

The pharmaceutical preparations of Tarceva® are formulations containing the hydrochloride salt. Tarceva® is supplied as tablets containing erlotinib hydrochloride equivalent to 150 mg, 100 mg, and 25 mg of erlotinib. All tablets are round, white, film-coated, bi-convex tablets without markings. Additional information regarding Tarceva® can be found in the Package Insert. Tarceva® tablets are supplied in blue-white, high-density polyethylene (HDPE) bottles of 30 tablets each.

5.1.2 Storage and Handling

Tarceva® tablets should be stored between 15°C and 30°C (59°F and 86°F).

5.1.3 Administration

Tarceva® tablets should be taken at approximately the same time of day. Each Tarceva® dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water, and should be taken 1 hour before or 2 hours after meals or medications, including grapefruit juice, vitamins, and iron supplements. The entire dose must be taken at one time. If the patient vomits after taking the tablet(s), the dose is replaced only if the tablet(s) can actually be seen and counted.

5.1.4 Potential Drug-Drug Interactions

Erlotinib is both protein bound (92% to 95% in humans) and metabolized in the liver by CYP3A4 and, to a lesser extent, CYP1A2, and in the lungs by CYP1A1. A potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 and CYP1A2 inhibitors/inducers.

For patients who are being concomitantly treated with a potent CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe adverse events. For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered.

Common CYP3A4 inhibitors include but are not limited to Amiodarone, Cannabinoids Miconazole, Erythromycin, Fluconazole, Norfloxacin, Fluoxetine, Omeprazole (slight), Quinine, Ritonavir, Indinavir, Ketoconazole, and Metronidazole. Common CYP3A4 inducers include but are not limited to Carbamazepine, Dexamethasone, Rifabutin, Ethosuximide, Rifampin, Phenobarbital, and Phenytoin.

In addition, altered coagulation parameters and bleeding have been reported in patients receiving erlotinib alone and in combination with other chemotherapeutic agents and concomitant warfarin-derivative anticoagulants. The mechanism for these alterations is still unknown. When warfarin is coadministered with erlotinib (anytime after Day 5), international

normalized ratio (INR) and prothrombin time should be closely monitored and the anticoagulant dose should be adjusted as clinically indicated.

5.2 **Pemetrexed** (ALIMTA)

5.2.1 Formulation

ALIMTA is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed. Each 500-mg vial of ALIMTA contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

5.2.2 Storage and Handling

ALIMTA, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

5.2.3 Administration

The recommended dose of ALIMTA is 500 mg/m2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. To reduce toxicity, patients treated with ALIMTA must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of ALIMTA; and dosing should continue during the full course of therapy and for 21 days after the last dose of ALIMTA. Patients must also receive one (1) intramuscular injection of vitamin B12 during the week preceding the first dose of ALIMTA and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as ALIMTA. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 mcg, and the dose of vitamin B12 was 1000 mcg. The most commonly used dose of oral folic acid in clinical trials was 400 mcg

5.2.4 Potential Drug-Drug Interactions

ALIMTA is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of ALIMTA. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of ALIMTA. Although ibuprofen (400 mg qid) can be administered with ALIMTA in patients with normal renal function (creatinine clearance ≥80 mL/min), caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA. In the absence of data regarding potential interaction between ALIMTA and NSAIDs longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

5.3 **Docetaxel**

5.3.1 Formulation

TAXOTERE (docetaxel) Injection Concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80. TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial.

5.3.2 Storage and Handling

Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.
After initial puncture, Docetaxel Injection multiple dose vials are stable for 28 days when stored between 2oC to 8oC and at room temperature, with or without protection from light.

5.3.3 Administration

Docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm3. In patients who experienced either febrile neutropenia, neutrophil < 500 cells /mm3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxeltherapy, the dose of docetaxel should be reduced from 100mg/m2 to 75mg/m2 and/or from 75 to 60mg/m2. If the patient continues to experience these reactions at 60mg/m2, the treatment should be discontinued.

5.3.4 Potential Drug-Drug Interactions

Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection, close monitoring for toxicity and a Docetaxel Injection dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided

5.4 **Gemcitabine**

5.4.1 Formulation

Gemzar (gemcitabine for injection, USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine. Gemzar (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing: 200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial - 1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial .

5.4.2 Storage and Handling

Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F).

5.4.3 Administration

Two schedules have been investigated and the optimum schedule has not been determined (see Clinical Studies (14.3)) Withthe 4-week schedule, Gemzar should be administered intravenously at 1000 mg/m2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. With the 3-week schedule, Gemzar should be administered intravenously at 1250 mg/m2 over 30 minutes on Days 1 and 8 of each 21-day cycle.

5.4.4 Potential Drug-Drug Interactions

No specific drug interaction studies have been conducted.

5.5 **Bevacizumab**

5.5.1 Formulation

Bevacizumab is available in 100 mg/4 mL single use vial (3) and 400 mg/16 mL, single use vials.

5.5.2. Storage and Handling

Avastin vials must be refrigerated at 2°C–8°C (36°F–46°F). Avastin vials should be protected from light. Store in the original carton until time of use. **DO NOT FREEZE. DO NOT SHAKE.** Diluted Avastin solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for up to 8 hours

5.5.3 Administration

Avastin should be diluted for infusion using aseptic technique. Withdraw the necessary amount of Avastin to obtain the required dose and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives. Inspect visually for particulate matter and discoloration prior to administration. **Avastin infusions should not be administered or mixed with dextrose solution. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. ADMINISTER ONLY AS AN IV SOLUTION.** Stop infusion if a severe adverse reaction occurs and administer appropriate medical therapy

5.5.4 Potential Drug-Drug Interactions
If used along with chemotherapy drugs known as anthracyclines, such as doxorubicin (Adriamycin), daunorubicin (Cerubidine, Daunomycin), epirubicin (Ellence), or mitoxantrone (Novantrone), this drug may increase the risk of congestive heart failure. Bevacizumab may cause irinotecan (Camptosar) to stay in the body longer, and may raise your risk of severe diarrhea. Bevacizumab given with carboplatin (Paraplatin) and paclitaxel (Taxol) may cause less paclitaxel to stay in the body. This may keep paclitaxel from working as it should. Any drugs or supplements that interfere with blood clotting can raise the risk of bleeding during treatment with bevacizumab.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1 Study Calendar

Study	Details	Pre-registration	During treatment	1 month follow-up[6]	3 month follow-up[6]	6 month follow-up[6]	Every 3, 6, or 12 months[7]
History, Physical Examination and Other Evaluations	• Medical history • Smoking history • Physical exam (PE) • Height • Weight • Vital signs • ECOG Performance status (PS)	All[1]	X[8]	• PE • Weight • Vital signs • PS	• PE • Weight • Vital signs • PS	• PE • Weight • Vital signs • PS	• PE • Weight • Vital signs • PS
Hematology	Complete blood count, platelets	X[1]	X[8]		X	X	X[4]
Liver function tests	• Total bilirubin • AST • ALT • Alkaline phosphatase	X[1]	X[8]		X	X	X[4]
Toxicities assessment	Graded per NCI CTCAE, v4.0	X[2]	X	X	X	X	X
Radiology	• CT scan of chest ,abdomen, and/or pelvis as clinically indicated •	X[3]			X	X	X[4]
	• Whole body PET/CT or • MRI	X[3]			X[4]	X[4]	X[4]
Maintenance chemotherapy usage			X	X[5]	X[5]	X[5]	X[5]

1. Within 21 days prior to registration.
2. Baseline evaluation should document any residual toxicity from previous therapy (SBRT-related Toxicities) .
3. Baseline studies within 90 days of registration; additional radiographic images of extra-hepatic, extra-pulmonary sites as clinically indicated. Imaging sufficient for inclusion in trial at time of enrollment includes diagnostic CT or PET/CT or MRI which demonstrates extent of metastatic disease.
4. Additional studies as clinically indicated.
5. If maintenance chemotherapy has been discontinued, date of stopping and reason (toxicity or disease progression) recorded.
6. Time from commencement of SBRT.
7. Every 3 months for year 1, every 6 months for years 2-3, and every 12 months for years 4-5.
8. Per standard of care for Maintenance chemotherapy

6.2 Follow-Up Schedule

All patients should be followed for study endpoints a minimum of 6 months. After 6 months, patients without progression should be followed according to Follow-Up table below. Clinical and laboratory evaluations will be performed according the Study Calendar in Section 6.1.

Clinical follow up will commence from the start of SBRT or maintenance chemotherapy.

Disease Status	Follow-up Schedule
Progression Free	Every 3 mos. for year 1 Every 6 mos. for years 2 -3 Every 12 mos. for years 4-5
Progression	Every 3 mos. for year 1 Every 6 mos. for years 2 -3

7. CRITERIA FOR STUDY DISCONTINUATION

Patients should be discontinued from the study in the following instances:

a. Inability to tolerate maintenance chemotherapy at prescribed dosing.
b. Disease Progression on maintenance chemotherapy. If the patient develops only a limited number of new discrete lesions potentially suitable for eradication with SBRT, the decision to continue maintenance chemotherapy or not would be made by the treating physicians based on whether the patient was otherwise clinically stable, tolerating maintenance chemotherapy without unacceptable toxicity, and wished to continue maintenance chemotherapy rather than either discontinue it or switch to another systemic agent. In such cases the PI should be notified, and documentation will be placed in the research chart that the new sites will be aggressively treated with additional SBRT
c. Other medical or ethical reasons, or noncompliance
d. Patient request

8. DATA AND SAFETY MONITORING

8.1 Data and Safety Monitoring Plan

8.1.1 Data Management and Monitoring/Auditing

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

For further information, refer to the UTSW SCCC IIT Management Manual.

Toxicity and dose escalation reviews will be performed annually. These reviews will be documented by written report and distributed to the study team.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

Adherence to the Protocol

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

- Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:
    - intentional on part of the investigator; or
    - in the investigator's control; or
    - not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

- Emergency Deviations: include any departure from IRB-approved research that is necessary to:
    - avoid immediate apparent harm, or
    - protect the life or physical well-being of subjects or others

    ➢ **Reporting requirement**: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

- Major Deviations (also called violations): include any departure from IRB-approved research that:
    - Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
    - Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

    ➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

- Minor Deviations: include any departure from IRB-approved research that:
    - Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
    - Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

8.1.2 Internal Data and Safety Monitoring Committee

The Radiation Oncology Clinical Research Office (CRO) reports serious adverse events (SAEs) to Radiation Oncology Data Safety Monitoring Committee (DSMC) monthly. These SAEs are also reported to the University of Texas Southwestern Medical Center (UTSW) IRB per IRB guidelines and SCC DSMC.

All clinical trials are reviewed on monthly basis for enrollment. These trials are assessed for safety on a continual basis throughout the life of the trial. For investigator-initiated trials, all SAEs are monitored – both local and at affiliated institutions.

A data safety monitoring committee including radiation oncologists not participating in this trial will be formed to review toxicity endpoints and efficacy data. In particular, this committee will scrutinize the grading of adverse events and the attribution to therapy previously assigned by the investigators. This panel will have access to basic patient information so as to have the ability to critically review toxicity events. This study will use this committee to perform ongoing safety assessment at regular defined intervals defined in the statistics section of this protocol. Unexpected toxicities occurring between defined interim analyses points will be reported to the treating center's IRB and also to the University of Texas Southwestern Institutional Review Board.

8.2 Adverse Events: Definitions and Reporting

Adverse Events will be reported as indicated by the appropriate following table (see below).

8.2.1 An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 30 days post treatment will be considered acute adverse events

Late Adverse Events (*as applicable*)

Adverse events occurring in the time period from the end of acute monitoring, to *5* years post treatment, will be defined as late adverse events. Radiation Oncology and Hematologic Oncology office notes will be reviewed for adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

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

Serious Adverse Events

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

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

8.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

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

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

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

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

8.2.3

Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

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

Note: This includes all events that occur *to the end of the acute adverse events reporting period as defined in section 8.2.1.* Any event that occurs *during the late adverse event period as defined in section 8.2.1* and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);

- the current Investigator's Brochure (if applicable)

the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

8.2.4 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

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

Written reports to: UTSW Radiation Oncology Clinical Research Manager Email: sarmistha.sen@utsouthwestern.edu Fax: 214-645-0780 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including

physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

9. EVALUATION OF PROGRESSION

Patients with evidence of new lesions amenable to SBRT during follow-up imaging not previously treated will be treated at the Radiation Oncologist's discretion. This will not constitute an event if the lesion is both amenable to SBRT and subsequently treated. However, if the lesion is not amenable to SBRT, the patient is either unwilling to pursue further treatment or cannot tolerate treatment due to coexisting comorbidities, then progression will be deemed to have occurred.

For liver lesions treated with SBRT, RECIST (Response Evaluation Criteria in Solid Tumors) criteria will be used for evaluation of progression. Evaluation of liver lesions within 3 months after SBRT is problematic and the appearance of non-enhancing hypodensity on follow-up CT scanning should not be mistaken for disease progression. For this reason a 6-month follow-up interval result is more reliable to evaluate progression. Measurable liver lesions are defined lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan. Complete response (CR) is the disappearance of the measurable target lesions on relevant imaging studies. Partial response (PR) is at least a 30% decrease in the sum of the longest diameter (LD) of measurable target lesions taking as reference the baseline sum LD. Progression (PD) is at least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Evaluation of lung lesions at any time after SBRT is difficult in view of the expected fibrotic reaction. Bone lesions seen only on PET are also not well scored by RECIST criteria and will

not be evaluated in that manner. For these reasons certain study-specific definitions of response and local control will apply. For lung lesions a complete response (CR) will be defined as the absence of abnormal metabolic activity on PET scan; a partial response (PR) will be defined as residual metabolic activity on PET scan in the absence of progressive disease. Fibrosis within the lung volume that receives a dose on the order of 18 Gy or more (typically 2-3 cm outside the PTV) has been commonly observed. The characteristic pattern is a gradual dissolution of a discrete mass and formation of a scar that recapitulates the shape of the radiation dose distribution. In this study progressive disease (PD) will be defined as residual increased metabolic PET scan in combination with expanded parenchymal opacity that retains mass-like discrete borders and extends outside the volume of lung that received at least 18 Gy.

All types of lesions will be scored at the six month time point for local control (LC) versus PD. LC for lung and liver lesions will be either CR or PR as described above. Progressive disease (PD) for bone lesions will be residual or increased metabolic activity on PET scan relative to baseline imaging with complementary CT or MRI that indicates residual solid tumor distinct from and lack of biopsy-proven pathologic fracture in the interim.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Primary Endpoint: Progression-free survival (PFS)

10.1.2 Secondary endpoints:

10.1.2.1 Rate in-field local control and rate of out-of-field disease progression.
10.1.2.2 Safety of SBRT with locally advanced or metastatic NSCLC after prior chemotherapy
10.1.2.3 Overall survival
10.1.2.4 Duration of maintenance of chemotherapy and time to initiation of third line systemic agent (chemotherapy or biologic agent)

10.2 Sample Size Determination

The sample size calculation is based on the primary endpoint, progression-free survival, and the assumption that patients are randomized until the end of accrual. The sample size is calculated with the 2-sided significance level of 0.1 and 80% statistical power using a two-sample log rank test. We assume that the progression-free survival function follows an exponential distribution for each arm. Accrual to the study is assumed to be uniformly distributed. The null hypothesis is that the there are no difference in median survival rates between two arms. We assume that patients will be accrued for 2 years with a 1-year follow-up. We hypothesize that the patients randomly assigned to the SBRT arm and maintenance chemotherapy arm have median PFS times of 10 months and 4 months, respectively, which is translated to the hazard ratio of 0.400. The total sample size of 36 patients (18 in the SBRT arm and 18 in the maintenance therapy arm) will be accrued to achieve the desired 80% statistical power and 2-sided significance level of 0.10. Sample size was estimated using the sample size software PASS 2008.

10.3 Patient Accrual

Patient accrual is projected to be 2 patients per month. This trial should complete the accrual phase in 24 months

10.4 Randomization Scheme
Patients will be allocated to the treatment using a randomized permuted block. There will be no stratification factor in randomization.

10.5 Analysis Plans
All eligible patients who are randomized to the study will be included in the comparison of treatment arms, regardless of treatment compliance (intent-to-treat analysis).
Progression-free survival time will be estimated using the Kaplan-Meier approach. The log-rank test will be used to test for a statistically significant difference in survival distributions. The null and alternative hypotheses are H_0: $S_1(t) = S_2(t)$ vs. H_A: $S_1(t) \neq S_2(t)$, where $S_i(t)$ is the distribution of progression-free survival times for patients in arm i. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference in progression-free survival. Unadjusted ratios and ratios adjusted for covariates of interest will be computed.

Overall survival will be analyzed in the same way as progression-free survival. In-field local control and rate of out-of-field disease progression will be estimated using the Kaplan-Meier approach.

For safety of SBRT, only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. The rates of all Grade 3-5 adverse events and death during or within 30 days of discontinuation of protocol treatment will be computed. Descriptive statistics will be computed for the duration of maintenance of chemotherapy, and time to initiation of third line systemic agent.

10.5.1 Stopping Rule
There will be an early stopping rule for unexpected toxicity. If at any point during the study more than 1/6 of patients treated to date experience study treatment-related grade 4-5 toxicity of any kind, study enrollment will be suspended. Depending on the nature of the toxicity and whether it is believed to be related maintenance chemotherapy or SBRT, the dose of one or the other might be modified by amendment to the protocol, which would require review and re-approval of the amended protocol by the IRBs of all participating institutions.

Please also see section 6.2 for clarification of start of primary endpoint.

11. DATA COLLECTION AND PATIENT REGISTRATION

The coordinating center for this trial will be UT-Southwestern. Patients can be registered only after eligibility criteria are met and approved by UTSW. For patients who pass screening, a completed patient registration form, which can be found in your forms binder, will need to be faxed with the provided cover sheet to: **Radiation Oncology Clinical Research, UT Southwestern, fax 214-648-5923.** UTSW will review the eligibility criteria to ensure eligibility and will fax back page 2 of the form which will contain PI signature and patient study number. If a patient is ineligible or if a waiver is granted, the enrolling institution will be notified of such decision which will include a brief explanation. Any waiver granted for patient eligibility is at the discretion of the Principal Investigator, Puneeth Iyengar, MD, PhD. Once patient has been deemed eligible by UTSW, the patient must be entered into the web database by the participating institution.

All subsequent data will be collected and entered into the web database as well. Supporting source documents for all data will be faxed to the following: **Radiation Oncology Clinical Research, UT Southwestern, fax 214-648-5923.** A training manual as well as onsite training will be provided for all participating institutions utilizing the web database. For patients enrolled at participating institutions, data will be collected and stored according to their institutional policies. The data will be kept in a secure location in accordance with prevailing HIPAA regulations. Adverse events will be reviewed and discussed at the monthly UTSW Department of Radiation Oncology Clinical Research monthly meetings in accordance with UTSW cancer center guidelines and meeting minutes will be made available to participating institutions.

12. RETENTION OF RECORDS

Documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence should be retained for at least 2 years after the investigation is completed.

13. APPENDICES

APPENDIX I: Smoker Status Case Report Form

XXXX ASSESSMENTS

CIGARETTE SMOKING HISTORY AT REGISTRATION

Date of evaluation: _____
DD MMM YYYY

1. Please indicate **one** of the following:
   - ☐ Subject never smoked cigarettes.
   - ☐ Subject has smoked < 100 cigarettes in a lifetime and stopped.
     Indicate when stopped: ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year
   - ☐ Subject has smoked > 100 cigarettes in a lifetime and stopped.
     Indicate when stopped: ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year
     Average number of cigarettes smoked per day: _____ Number of years smoked: _____
   - ☐ Subject is currently smoking cigarettes.
     Average number of cigarettes smoked per day: _____ Number of years smoked: _____

OTHER TOBACCO/NICOTINE HISTORY AT REGISTRATION

1. Please indicate **one** of the following:
   - ☐ Subject **never** used other tobacco or nicotine products. ***Do not*** *complete question 2.*
   - ☐ Subject **currently or in the past** has used other tobacco or nicotine products. *Complete question 2.*
2. If a user of tobacco/nicotine products, indicate frequency used and/or how long ago product use stopped.

Cigars/Pipes ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

Oral Tobacco Products ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

Nicotine Replacement Therapy ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

Other, please specify: _____ ☐ Not Applicable
Frequency used: ☐ at least once daily ☐ at least once weekly ☐ at least once monthly
Product stopped: ☐ current ☐ < 1 month ☐ 1 month-1 year ☐ > 1 year

APPENDIX II: Known Risks of Medications

II.I Tarceva

Respiratory

Respiratory side effects have included reports of serious interstitial lung disease, including fatalities in the treatment of non-small cell lung cancer or other advanced solid tumors. Dyspnea (41%) and cough (33%) have also been reported.

Dermatologic

Dermatologic side effects including rash (75%), pruritus (13%), dry skin (12%), alopecia, hirsutism, eyelash/eyebrow changes, paronychia, and brittle and loose nails have been reported. Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Cases of rosacea-like folliculitis and Malassezia sympodialis have also been reported.

Treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

The appearance of a rash in cancer patients treated with erlotinib is strongly associated with longer survival, according to researchers from the drug's developer, OSI Pharmaceuticals, Inc.

Rash resulted in study discontinuation in 1.2% patients. Dose reduction or interruption for rash was needed in 5.1% of patients. In erlotinib-treated patients who developed rash, the onset was within two weeks in 66% and within one month in 81%.

Gastrointestinal

The median time to onset of diarrhea was 12 days. Diarrhea resulted in study discontinuation in 0.5% of patients. Dose reduction or interruption for diarrhea was needed in 2.8% of patients.

Patients receiving concomitant antiangiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at an increased risk for gastrointestinal perforation. Erlotinib (the active ingredient contained in Tarceva) should be permanently discontinued in patients who develop gastrointestinal perforation.

Gastrointestinal side effects including diarrhea (54%), nausea (33%), vomiting (23%), stomatitis (17%), and abdominal pain (11%) have been reported. Gastrointestinal perforation has been reported in patients receiving erlotinib, including fatalities. Gastrointestinal bleeding has been reported infrequently.

Hepatic

Hepatic side effects including hepatic failure, hepatorenal syndrome, and liver function test abnormalities such as elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin have been reported. A case of hepatitis has also been reported.

These elevations were mostly transient or associated with liver metastases.

A pharmacokinetic study in patients with advanced solid tumors and moderate hepatic impairment according to the Child-Pugh criteria has been reported. In this study, 10 of the 15 patients died on treatment or within 30 days of the last erlotinib dose. Eight of these patients died from progressive disease, one patient died from hepatorenal syndrome, and one patient died from rapidly progressing liver failure. Six out of the 10 patients who died had baseline total bilirubin greater than 3 times the upper limit of normal suggesting severe, rather than moderate, hepatic impairment. All patients had hepatic impairment due to advanced cancer with liver involvement such as hepatocellular carcinoma, cholangiocarcinoma, or liver metastases.

Patients with hepatic impairment should be monitored closely during therapy with erlotinib, and dosing should be interrupted or discontinued if changes in liver function are severe.

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent erlotinib 150 mg in the Maintenance study. Grade 2 (>2.5 - 5 x ULN) ALT elevations occurred in 2% and 1%, and Grade 3 (>5 - 20 x ULN) ALT elevations were observed in 1% and 0% of erlotinib and placebo treated patients, respectively. The erlotinib treatment group had Grade 2 (>1.5-3 x ULN) bilirubin elevations in 4% and Grade 3 (>3-10 x ULN) in <1% compared with <1% for both Grades 2 and 3 in the placebo group.

General

General side effects including anorexia (52%) and fatigue (52%) have been reported.

Immunologic

Immunologic side effects including infection (24%) have been reported.

Ocular

Ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca, or keratitis are known risk factors for corneal ulceration/perforation.

Erlotinib (the active ingredient contained in Tarceva) therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Ocular side effects including conjunctivitis (12%), keratoconjunctivitis sicca (12%), corneal perforation and ulceration, abnormal eyelash growth, and keratitis have been reported.

Renal

Renal side effects including cases of hepatorenal syndrome, acute renal failure or renal insufficiency (some with fatalities) have been reported.

Other

Other side effects including a case of bilateral eardrum perforation have been reported.

II.II Pemetrexed

Gastrointestinal

Gastrointestinal side effects including nausea (84%), vomiting (58%), constipation (44%), anorexia (35%), stomatitis/pharyngitis (28%), diarrhea without colostomy (26%), dehydration (7%), and dysphagia/esophagitis/odynophagia (6%) have been reported. Colitis has been reported rarely.

General

General side effects including fatigue (80%), chest pain (40%), fever (17%), other constitutional symptoms (11%), and edema have been reported.

Respiratory

Respiratory side effects including dyspnea (66%) and interstitial pneumonitis have been reported.

Hematologic

Hematologic side effects including neutropenia (58%), leukopenia (55%), anemia (33%), and thrombocytopenia (27%) have been reported.

Dermatologic

Dermatologic side effects including rash/desquamation (22%) and asteatotic eczema have been reported.

Nervous system

Nervous system side effects including neuropathy/sensory effects (17%) have been reported.

Renal

Renal side effects including creatinine elevation (16%), and renal failure (2%) have been reported.

Psychiatric

Psychiatric side effects including mood alterations/depression (14%) have been reported.

Cardiovascular

Cardiovascular side effects including thrombosis/embolism (7%) have been reported.

Immunologic

Immunologic side effects including infection without neutropenia (1%), infection with grade 3 or grade 4 neutropenia (6%), infection/febrile neutropenia-other (3%), and febrile neutropenia (1%) have been reported.

Hypersensitivity

Hypersensitivity side effects including allergic reactions (2%) have been reported.

Other

Side effects below show the incidence of CTC grade 3/4 toxicities in patients who received both pemetrexed and cisplatin along with vitamin supplementation including daily folic acid and vitamin B12. Other side effects including radiation recall have been reported in patients who have previously received radiotherapy.

II.III Docetaxel

Hematologic

Hematologic side effects including bone marrow suppression have been the major dose-limiting toxicity. A reversible and not cumulative neutropenia has also been reported. A median of 8 days to nadir and median duration of severe neutropenia (less than 500 cells/mm3) of 7 days has been reported. A fatal gastrointestinal hemorrhage associated with thrombocytopenia has been reported in one patient. Three patients with severe liver dysfunction developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported during postmarketing experience.

Patients carrying the GSTP1 A/B and 3435TT genotypes may have excessive hematologic toxicity.

In a summary of 37 clinical trials (n = 1,495), neutropenia (less than 2,000 cells/mm3) has been reported in 96.3% of patients with normal LFTs at baseline and 96% of patients with elevated LFTs. Neutropenia (less than 500 cells/mm3) has been reported in 76% of patients with normal LFTs at baseline and 86% of patients with elevated LFTs.

Leukopenia (less than 4,000 cells/mm3) has been reported in 96.5% of patients with normal LFTs at baseline and 98.1% of patients with elevated LFTs. Leukopenia (less than 1,000 cells/mm3) has been reported in 31% of patients with normal LFTs at baseline and 44.2% of patients with elevated LFTs. Thrombocytopenia (less than 100,000 cells/mm3) has been reported in 7.5% of patients with normal LFTs at baseline and 27.3% of patients with elevated LFTs.

Anemia (less than 11 g/dL) has been reported in 89.5% of patients with normal LFTs at baseline and 92.7% of patients with elevated LFTs. Anemia (less than 8 g/dL) has been reported in 8.4% of patients with normal LFTs and 30.9% of patients with elevated LFTs.

Febrile neutropenia has been reported in 11.8% of patients with normal LFTs at baseline and 26.4% of patients with elevated LFTs.

Hypersensitivity

In one institution's experience with 623 courses of docetaxel therapy (n = 168), hypersensitivity reactions decreased from 50% to 5% once patients began receiving systemic prophylaxis including corticosteroids and antihistamines.

Hypersensitivity side effects may occur within a few minutes following initiation of a docetaxel infusion. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm,

or generalized rash/erythema occurred in 0.9% of patients who received the recommended dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of therapy have been reported in 5 of 1260 patients who did not receive premedication. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever or chills have also been reported and resolved after discontinuation of the infusion and initiation of appropriate therapy. Bullous eruption including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Rare cases of anaphylactic shock have been reported during postmarketing experience. Very rarely, these cases resulted in a fatal outcome in patients who received premedication.

General

General side effects including diffuse pain, chest pain, and radiation recall phenomenon have been reported.

Severe adverse events have been reported in 49% of patients treated with docetaxel 60 mg/m2 compared to 55.3% and 65.9% treated with 75 mg/m2 and 100 mg/m2 respectively. Discontinuation due to adverse events was reported in 5.3% of patients treated with 60 mg/m2 versus 6.9% and 16.5% for patients treated at 75 mg/m2 and 100 mg/m2 respectively. Deaths within 30 days of last treatment occurred at a rate of 4.0% in patients treated with 60 mg/m2 compared to 5.3% and 1.6% for patients treated at 75 mg/m2 and 100 mg/m2 respectively.

Cardiovascular

Cardiovascular side effects including hypotension have been reported in 3.6% of patients (3.4% required treatment). Heart failure, sinus tachycardia, atrial fibrillation, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, myocardial infarction, and hypertension have also been reported.

Renal

Renal side effects including severe fluid retention (generally renal in origin and generally after four to five courses of therapy) have been reported in patients using a five day dexamethasone premedication regimen. The fluid retention was characterized by one or more of the following events; poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites). Renal insufficiency has been reported during postmarketing experience with the majority of these cases associated with concomitant nephrotoxic drugs.

Moderate fluid retention (17.4%), severe fluid retention (6%) and discontinuation (1.7%) have been reported among 229 patients with normal liver function using a five day dexamethasone premedication regimen. Fluid retention was completely, but sometimes slowly reversible resolving in a median of 29 weeks following discontinuation. The median cumulative dose to the onset of moderate or severe fluid retention was 705 mg/m2 (in patients receiving premedication). In a summary of 37 clinical trials (n = 1,495), fluid retention was reported in 48.5% of patients with normal LFTs at baseline and 66.7% of patients with elevated LFTs. In the same trials, severe fluid retention was reported in 5.2% of patients with normal LFTs at baseline and 33.3% of patients with elevated LFTs. Patients developing peripheral edema may be treated with standard measures including salt restriction, diuretics (e.g. spironolactone), etc.

Nervous system

Spontaneous reversal of symptoms occurred in a median of 9 weeks from onset. Approximately 3.8% of the 134 patients required discontinuation of therapy due to neurotoxicity. In a summary of 37 clinical trials (n = 1,495), neurosensory symptoms were reported in 53.7% of patients with normal LFTs at baseline and 41.8% of patients with elevated LFTs. In the same trials, severe neurosensory symptoms were reported in 3.9% of patients with normal LFTs at baseline and none of the patients with elevated LFTs. In a study (n = 46) of 209 cycles, peripheral neurotoxicity was reported in 30% of patients. In another study (n = 186), 11% of patients developed mild to moderate sensory neuropathy at cumulative doses ranging from 50 to 750 mg/m2 and doses of 10 to 115 mg/m2.

Nervous system side effects including paresthesia, dysesthesia, and pain (7%) have been reported in one study (n = 134). Confusion and rare cases of seizures or transient loss of consciousness have been reported, sometimes appearing during the infusion of the drug.

Hepatic

Hepatic side effects including various increases in blood levels have been reported. In patients with normal LFTs at baseline, bilirubin values greater than the upper limit of normal (ULN) occurred in 8.9% of patients. Increases in SGOT or SGPT greater than 1.5 times the ULN, or alkaline phosphatase greater than 2.5 times the ULN were observed in 18.1% and 7.6% of patients, respectively. Increases in SGOT and/or SGPT greater than 1.5 times the ULN concomitant with alkaline phosphatase greater than 2.5 times the ULN occurred in 4.5% of patients with normal LFTs at baseline. Rare cases of hepatitis have been reported during postmarketing experience.

Gastrointestinal

In a summary of 37 clinical trials (n = 1,495), nausea has been reported in 40.4% of patients with normal LFTs at baseline and 40% of patients with elevated LFTs. Diarrhea has been reported in 40.4% of patients with normal LFTs at baseline and 32.7% of patients with elevated LFTs. Vomiting has been reported in 24% of patients with normal LFTs at baseline and 25.5% of patients with elevated LFTs. Severe GI reactions were reported in 8.2% of patients.

Stomatitis has been reported in 42.3% of patients with normal LFTs at baseline and 47.3% of patients with elevated LFTs. Severe stomatitis has been reported in 5.3% of patients with normal LFTs at baseline and 14.5% of patients with elevated LFTs. Stomatitis appears to be dose dependent.

Gastrointestinal (GI) side effects including nausea, vomiting, diarrhea, stomatitis abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, GI hemorrhage, GI perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis, ischemic colitis, and dehydration as a consequence to GI events have been reported.

Dermatologic

Dermatologic side effects including reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face or thorax (and usually associated with pruritus) have been reported. Severe hand and foot syndrome has been reported. Severe nail disorders (2.6%), alopecia, and localized erythema of

the extremities with edema followed by desquamation have also been reported. Very rare cases of cutaneous lupus erythematosus have been reported. Scleroderma-like changes usually preceded by peripheral lymphedema have been reported. One case of supravenous discoloration of the skin due to docetaxel treatment has been reported.

Eruptions generally occurred within one week after dosage administration and were not disabling. Recovery generally occurred before the next infusion.

In a summary of 37 clinical trials (n = 1,495), cutaneous adverse events have been reported in 58.5% of patients with normal LFTs at baseline and 61.8% of patients with elevated LFTs. In the same trials, severe cutaneous adverse events have been reported in 5.6% of patients with normal LFTs at baseline and 10.9% of patients with elevated LFTs. The discontinuation rate due to skin toxicity was 1.7%. Alopecia has been reported in 80% of patients with normal LFTs at baseline and 61.8% of patients with elevated LFTs. In one study (n = 46) of 209 cycles, alopecia was reported in 91% of patients. In one institution's experience with 623 courses of docetaxel therapy (n = 168), dermatologic toxicity decreased from 53% to 14% once patients began receiving systemic prophylaxis including corticosteroids and antihistamines.

Severe nail disorder were characterized by hypo- or hyperpigmentation and occasionally by onycholysis (0.8%) and pain.

Local

Local side effects consisting of infusion site reactions have been reported. These reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation or swelling of the vein. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported during postmarketing experience. These were reversible upon discontinuation of the infusion.

Other

In a summary of 37 clinical trials (n = 1,495), asthenia has been reported in 61.5% of patients with normal LFTs at baseline and 54.5% of patients with elevated LFTs. In the same trials, severe asthenia has been reported in 11.1% of patients with normal LFTs at baseline and 23.6% of patients with elevated LFTs. In a study (n = 46) of 209 cycles, malaise was reported in 52% of patients.

Other side effects have included asthenia (11.1% to 61.5%) and malaise (52%). Fatigue and weakness have been reported to have lasted a few days to several weeks and were occasionally associated with deterioration of performance status in patients with progressive disease. Rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs. A case of docetaxel-induced recall dermatitis on previous laser treatment sites has also been reported.

Ocular

Ocular side effects including conjunctivitis and lacrimation have been reported. Canalicular and nasolacrimal duct obstruction has been a common side effect of weekly docetaxel therapy and has even been reported to occur when docetaxel is used in the neoadjuvant setting according to one study. Excessive tearing which may be attributable to lacrimal duct obstruction has also been reported.

Respiratory

Respiratory side effects including dyspnea, acute pulmonary edema, acute respiratory distress syndrome, and interstitial pneumonia have been reported. Pulmonary fibrosis has been rarely reported.

II.IV Gemcitabine

Hematologic

Myelosuppression is the major dose-limiting factor associated with gemcitabine therapy.

Dosage adjustments for hematologic toxicity are frequently necessary. Less than 1% of patients have had to discontinue therapy for either anemia, leukopenia, or thrombocytopenia. Grade 3/4 thrombocytopenia was more common in the elderly, especially older women.

The risk for thrombotic thrombocytopenic purpura increases as the cumulative dose of gemcitabine approaches 20,000 mg/m2.

Hematologic side effects including anemia (68%), leukopenia (62%), neutropenia (63%), thrombocytopenia (24%), petechiae (16%), thrombotic thrombocytopenic purpura (0.015% to 1.4%), and sepsis (less than 1%) have been reported. Red blood cell transfusions were required by 19% of patients.

Gastrointestinal

Gastrointestinal side effects including nausea and vomiting (69%), diarrhea (19%) and stomatitis (11%) have been reported. A case of severe anal pruritus has also been reported.

If the patient is not vomiting due to their disease state, nausea can generally be prevented by administration of prochlorperazine or low-dose oral serotonin antagonists and glucocorticoid therapy. One study of 790 patients found the rate of WHO grade 3 nausea and vomiting at a frequency of 22% in patients under 65 years of age, and 12% in patients 65 years of age or older.

Hepatic

No evidence of increased hepatic toxicity has been reported with longer duration or greater total cumulative dose.

Hepatic side effects including transient elevations in ALT (68%), AST (67%), alkaline phosphatase (55%), bilirubin (13%), and GGT have been reported. Serious hepatotoxicity including liver failure and death have been reported very rarely.

Renal

Renal side effects including proteinuria (45%), hematuria (35%), renal failure, hemolytic-uremic syndrome (0.25%), and nephrotoxicity have been reported.

Renal failure may not be reversible, even upon discontinuation of therapy.

Other

The flu-like symptoms usually take place a few hours after drug administration. The symptoms are usually self-limiting and recovery is generally within 24 to 48 hours. Less than 1% of patients discontinued use due to flu-like symptoms. Some patients get relief from nonsteroidal anti-inflammatory drugs or acetaminophen.

Out of the five reported cases of distal ischemic changes, four of those case related to combination chemotherapy with cisplatin and gemcitabine, while one case was of gemcitabine as a single agent in first-line therapy.

Other side effects including fever (41%), frequently associated with other flu-like symptoms, has been reported. There was a 16% incidence of infection among the patients with fever. Both fever and asthenia have frequently been reported as isolated effects. Flu syndrome (19%), including fever, asthenia, anorexia, headache, cough, chills, and myalgia has been reported. Insomnia, rhinitis, sweating, and malaise have been reported infrequently. Vasculitis and gangrene have been reported very rarely. Five cases of distal ischemic changes have been reported.

A pattern of tissue injury typically associated with radiation toxicity has also been reported in association with the use of gemcitabine.

Dermatologic

Rash was generally a macular or finely granular maculopapular pruritic eruption, mild to moderate in severity, involving the trunk and extremities. Alopecia is usually minimal.

Dermatologic side effects including rash (30%), alopecia (15%), pruritus (13%), and radiation recall have been reported. Cellulitis has been reported rarely. Severe skin reactions including desquamation and bullous skin eruptions have been reported very rarely. Two cases of pseudocellulitis have been reported. A case of linear immunoglobulin A bullous dermatosis has also been reported.

Respiratory

Some of the dyspnea reported may have been due to underlying disease. Forty percent of the study population consisted of lung cancer patients, while some of the other study patients had pulmonary manifestations of other malignancies.

Different patterns of lung injury may be related to gemcitabine. A rapid response following the administration of corticosteroids would mean the respiratory problem was probably due to a hypersensitivity reaction.

Respiratory side effects including dyspnea (23%), sometimes accompanied by bronchospasm (<2%) have been reported. Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome has been reported rarely. Respiratory failure and death have been reported very rarely (in some patients, despite the discontinuation of therapy).

Nervous system

Less than 1% of the paresthesias have been severe.

Nervous system side effects including paresthesias (10%) have been reported.

Local

Local side effects including "injection-site-related events" (4%) have been reported by the manufacturer.

Hypersensitivity

Hypersensitivity side effects including anaphylactoid reactions have been reported rarely.

Cardiovascular

Many of the patients that suffered cardiovascular effects had a prior history of cardiovascular disease. Two percent of patients discontinued therapy due to these effects. Less than 1% of patients discontinued due to edema.

Cardiovascular side effects including peripheral edema (20%), edema (13%), cerebrovascular accident, hypotension, hypertension, and generalized edema (less than 1%) have been reported. Atrial fibrillation has been reported rarely. Congestive heart failure, myocardial infarction, and arrhythmias (predominantly supraventricular in nature) have been reported very rarely.

Immunologic

Immunologic side effects including a scleroderma-like reaction have been reported.

Oncologic

Long term animal studies to evaluate carcinogenic potential have not been conducted.

Oncologic side effects have been reported in animal studies. Gemcitabine induced forward mutations in vitro in a mouse lymphoma assay and was clastogenic in an in vivo micronucleus assay.

II. V Bevacizumab

Gastrointestinal

Non-Gastrointestinal Fistula Formation: Discontinue Avastin if fistula formation occurs

Renal

Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Temporarily suspend Avastin for moderate proteinuria.

Other

Ovarian Failure: Inform females of reproductive potential of the risk of ovarian failure with Avastin

Nervous system

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Discontinue Avastin.

Cardiovascular

Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend Avastin if not medically controlled. Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy. Arterial Thromboembolic Events (e.g., myocardial infarction, cerebral infarction): Discontinue Avastin for severe ATE.

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