Single-Arm Phase II Study of Stereotactic Body Radiation Therapy Concurrent with Nelfinavir for Oligometastases

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Principal Investigator	Phuoc tran, MD, M.D. Sidney Kimmel Comprehensive Cancer Center Johns Hopkins University Weinberg Building 401 N. Broadway, Suite 1440 Baltimore, MD 21231 Phone: 410-614-3880 Fax: 410-502-1419 Email: tranp@jhmi.edu
Co-Investigators	Russell Hales, M.D. Lawrence Kleinberg, M.D. Danny Song, M.D. Michael Lim, M.D. Fariba Asrari, M.D. Shirl DiPasquale, RN
Statistician	Hao Wang
Research Managers:	Dana Kaplin Terry Caldwell

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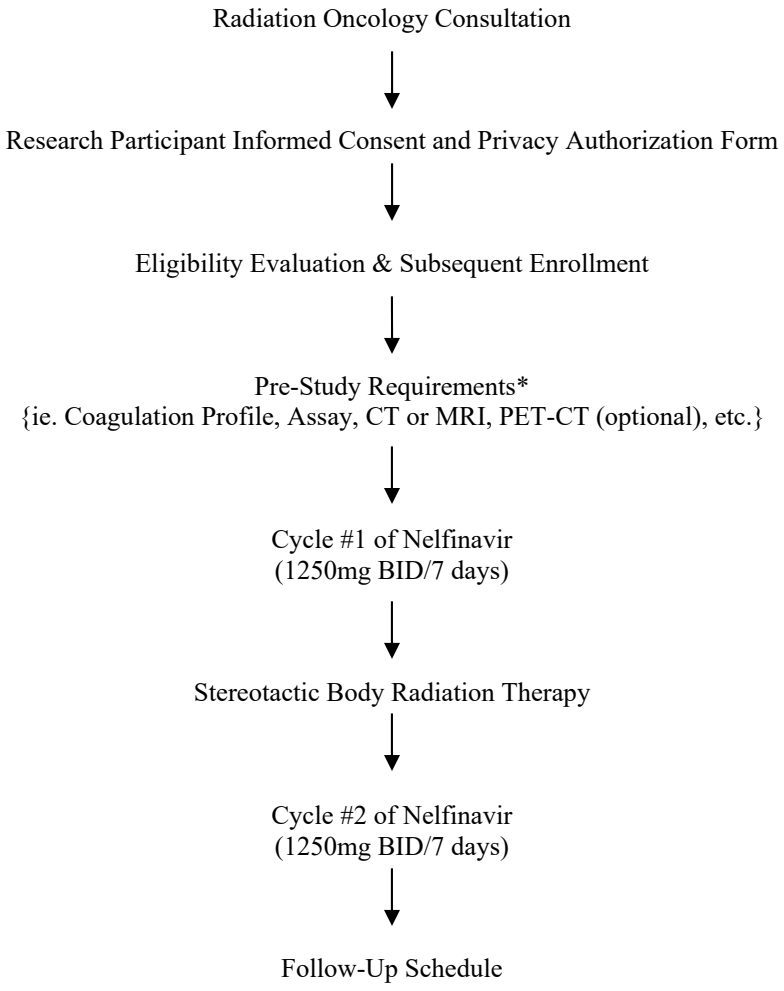

*Pre-Study Requirements are specific to each patient
* If scheduling or safety prevents all lesions from being irradiated within one day, participants will complete Cycle #2 of Nelfinavir then undergo a minimum of 7 days “clear out”. Following this break participants will repeat Cycle #1 of Nelfinavir then receive radiation to the remaining lesions followed by a repeat Cycle #2 of Nelfinavir. This process may not exceed three “rounds” of treatment (NFV1, SBRT, NFV2) and may include repeat imaging and/or blood work.

1. PROTOCOL SYNOPSIS

TITLE	Single-Arm Phase II Study of Stereotactic Body Radiation Therapy Concurrent with Nelfinavir for Oligometastases
STUDY PHASE	Phase II
INDICATION	Patients presenting with oligometastatic disease, where metastases are limited in number and location.
PRIMARY OBJECTVES	• To determine the 6-month freedom from local progression rate of the radiosensitizer Nelfinavir used concurrently with 15 Gy of stereotactic body radiation therapy (SBRT) delivered in 1 fraction (per lesion) in patients with oligometastatic disease
SECONDARY OBJECTIVES	• To assess the toxicity of the radiosensitizer Nelfinavir used concurrently with 15 Gy of stereotactic body radiation therapy (SBRT) delivered in 1 fraction(per lesion) in patients with oligometastatic disease • To determine local control at 6 months after SBRT delivered to a dose of 15 Gy in 1 fraction (per lesion) combined with Nelfinavir in patients with oligometastatic disease • To assess long-term clinical outcomes of this patient population after completion of SBRT in combination with Nelfinavir • To assess quality of life following completion of SBRT in combination with Nelfinavir • To determine the correlation between phospho-Akt levels and lesion response rate
HYPOTHESES	Concurrent SBRT and Nelfinavir will achieve greater than 70% freedom from local progression 6 months.
STUDY DESIGN	Patients with metastatic lesions of the lung, liver, or bone will be candidates for treatment. Within three weeks of the initial treatment planning, a 15 Gy dose (per lesion) of SBRT will be administered. Prior to SBRT, patients will initiate Nelfinavir oral therapy twice daily for 7 days. Once SBRT is completed, the patient will repeat the same Nelfinavir therapy for an additional 7 days for a total of 14 days of treatment.
SAMPLE SIZE BY TREATMENT GROUP	42 patients total
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	1. Metastasis at one or more of the following sites: bone, liver, and/or lung. No more than 5 lesions will be treated. 2. Tumor(s) to be treated is(are) ≤ 5.0 cm or ≤ 250 cm^3. 3. Age ≥ 18 years. 4. ECOG perfomance status ≤ 2. 5. Histologic confirmation of malignancy (primary or metastatic tumor).

INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION	Commercially available Nelfinavir (1250 mg) will be administered orally twice daily for 14 days.
CONTROL GROUP	N/A
PROCEDURES	1. Physical exam 2. Blood draw 4. CT or MRI of Involved Site 5. PET-CT (all are optional) 6. SBRT + oral Nelfinavir administration

2. ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	**Definition**
ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
MTD	Maximum tolerated dose
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event

Abbreviation	Definition
SBRT	Stereotactic body radiation therapy
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

3. OBJECTIVES

3.1 Primary Objective

To determine the 6-month freedom from local progression rate of the radiosensitizer Nelfinavir used concurrently with 15 Gy of stereotactic body radiation therapy (SBRT) delivered in 1 fraction (per lesion) in patients with oligometastatic disease.

3.2 Secondary Objectives

To assess the toxicity of the radiosensitizer Nelfinavir used concurrently with 15 Gy of stereotactic body radiation therapy (SBRT) delivered in 1 fraction (per lesion) in patients with oligometastatic disease.

To determine local control at 6 months after SBRT delivered to a dose of 15 Gy in 1 fraction (per lesion) combined with Nelfinavir patients with oligometastatic disease.

To assess long-term clinical outcomes of this patient population after completion of SBRT in combination with Nelfinavir.

To assess quality of life following completion of SBRT in combination with Nelfinavir.

To determine the correlation between Phospho-Akt levels and lesion response rate.

4. BACKGROUND

4.1 Oligometastatic Disease

Cancer is the second leading cause of death in the United States, chiefly from an inability to control metastatic disease. Systemic therapy alone is not curative for patients with most metastatic solid tumors.(1) The metastatic capacity of cancers behaves along a spectrum of disease progression, such that some tumors have spread widely before clinical detectability and others never metastasize. Contained within this spectrum, is an oligometastatic state where metastases are limited in number and location. The presence of an oligometastatic state was originally proposed by Hellman who suggested that these oligometastatic patients would benefit from effective local therapy in addition to systemic therapy.(1) In agreement with this hypothesis, surgery and chemotherapy for isolated pulmonary metastases can result in long term disease-free periods. (2) Additionally, some 25% of patients following

resection and chemotherapy for colorectal cancer and isolated liver metastases can similarly have long-term disease free survival.(3)(4)(5)

The treatment of metastases depends on multiple factors including 1) the location of the primary tumor, 2) the presence or absence of other metastatic foci, 3) the size, number and location of metastases, 4) the effectiveness of various forms of therapy (such as surgery, radiation and chemotherapy), and 5) patient's functional status. Extracranial metastatic tumors most often referred for local therapy in the form of resection include colon cancer, sarcomas, germ cell tumors, and melanoma metastatic to the lung. For the more common primary tumors such as those of breast and lung, metastases are rarely referred for resection as chemotherapy (or hormonal manipulation) is generally considered to be the primary mode of treatment.

4.2 Stereotactic Body Radiation Therapy (SBRT)

Conventional moderate dose radiation for metastatic disease is given primarily for palliation. Recent advancements in radiation delivery now make it possible to image and treat precisely within any anatomical region of the body.(6, 7) As a result, the capacity to deliver tumor killing radiation doses in a single or few (1-5) outpatient radiation treatments is now possible.(8-12) In addition, by minimizing the irradiation of surrounding healthy tissue, it should also be possible to decrease the rate of complications. Intracranial stereotactic body radiation therapy (SBRT) has been shown to be a highly effective treatment for brain metastases.(13) This suggests that selective small extracranial tumors (either primary or metastatic tumors) may be effectively controlled by similar focal high-dose SBRT. There is an increasing experience with extracranial SBRT as effective local therapy for metastatic lesions. Local control in excess of 75% has been reported for metastatic tumors of the spine, lung and liver, which is significantly higher than standard conventional moderate dose radiation.(9, 11, 12, 14)(15) Toxicity has been minimal in multiple U.S., European and Japanese trials of extracranial stereotactic radiotherapy to the lung, liver, spine, pelvis and abdomen despite the use of very high biological equivalent doses for patients with both organ confined and metastatic cancer.

4.3 Tumor Hypoxia

Another factor potentially limiting the efficacy of SBRT or hypofractationated regimens is intratumoral hypoxia. Tumor hypoxia is a well substantiated poor prognostic factor for multiple tumor types and increases tumor cell radioresistance. A several week course of fractionated radiation therapy can partially mitigate tumor hypoxia because death of well oxygenated tumor cells allows for reoxygenation of more hypoxic clonogens in a tumor. The efficacy of SBRT or hypofractionated regimens are suscetible to tumor hypoxia because treatment is delivered in an abbreviated course not allowing for tumor reoxygenation. A normoxic and hypoxic tumor selective radiosensitizer in combination with SBRT would hypothetically overcome barriers to intratumoral hypoxia.

4.4 Nelfinavir

A compound ideally situated to meet the requirements as a normoxic and hypoxic tumor selective radiosensitizer is the HIV protease inhibitor Nelfinavir. The first report of an antitumoral activity of an HIV protease inhibitor (HPI) was published in 1999 as a case

report. The normoxic radiosensitizing effect of Nelfinavir has been well characterized *in vitro* and *in vivo* and has been linked to the inhibition of phospho-Akt which is overexpressed in many different types of solid tumors, but not normal tissues. Nelfinavir can radiosensitize hypoxic cells within a tumor by decreasing HIF-1α expression and vascular endothelial growth factor (VEGF) release resulting in angiogenesis inhibition and improved tumor oxygenation. Nelfinavir also sensitizes endothelial cells to radiation-induced death. Finally, utilization of Nelfinavir (Viracept; F. Hoffmann-La Roche Ltd, Basel, Switzerland) as an anticancer agent would have the advantage that the drug has already been used for more than a decade in the clinic and its safety profile is well defined. Retrospective data from HIV positive patients taking routine doses of HPIs concurrently during conventional radiation therapy suggests no increased normal tissue toxicity. (37, 38)

4.5 Rationale for Use in Pulmonary Metastasis

Pulmonary tissue represents a fertile area for metastatic seeding from epithelial malignancies. Aggressive management with surgical resection has resulted in good outcomes. For example, in the International Registry of Lung Metastases, over 5000 cases of lung metastasectomy are recorded.

Multiple series have shown local control for primary lung tumors of >90% using stereotactic body radiotherapy in medically inoperable patients.(16-19)(20) A related series compared outcomes of wedge resection versus SBRT in primary lung cancer and found improved local control with SBRT.(21) These studies report acceptable toxicity profiles with a low risk of grade III or greater toxicity. Consequently, two randomized trials are investigating the role of SBRT versus surgery in medically fit patients. This includes the Dutch ROSEL trial which randomizes operable stage T1N0 patients to surgery versus SBRT as well as the STARS trial which randomizes operable stage 1 (<4cm) patients to surgery versus SBRT.

Taken together, less invasive techniques such as SBRT are now being applied in place of metastasectomy in oligometastatic disease to target pulmonary metastasis. Multiple institutions have reported favorable outcomes using either single or multi-fraction SBRT for oligometastatic sites within the lung. Wulf et al. prescribed 26 Gy in single fraction and reported a 90% local control at 9 months.(22) Hof and colleagues report 63% progression free survival at 3 years using 12-30 Gy prescribed to the isocenter.(23) Le treated primary early stage and metastatic lung tumors with SBRT using doses of 15-30 Gy and report a local control of 91% for doses greater than 20 Gy and 54% for doses less than 20 Gy.(11)

Single dose fraction of 15 Gy with SBRT to the lung is used to allow for acceptable toxicity and to meet dose constraints when multiple pulmonary targets are treated. Single dose SBRT is limited by treatment toxicity at higher doses. Le and colleagues report a 12.5% rate of grade 2 to 3 pneumonitis and a 9.4% rate of possible treatment related death when single SBRT doses of greater than 25 Gy were given. However, toxicity was rare when doses of less than 25 Gy were given.(11) The potential for multiple targets in the oligometastatic setting results in difficulty in achieving pulmonary tissue constraints when

doses of >25 Gy are applied to each target. An attractive alternative is to dose reduce radiation while giving a radiation sensitizer.

A dose of 15 Gy will allow for safe targeting of multiple pulmonary metastases. Radiosensitizing effects of Nelfinavir may improve local control to mirror those results with higher dose radiation while providing acceptable toxicity. To date, there is no literature to suggest an increased rate of pneumonitis or other pulmonary toxicity with concurrent administration of Nelfinavir and radiation.

Reports of SBRT in pulmonary metastasis are heterogeneous. Most reports of metastatic lung tumors include medically inoperable patients with a primary lung malignancy. While some groups report equivalent outcomes, others reports decreased local control with metastatic versus primary lung cancer. For example, Le et al., report a 1 year freedom from local relapse of 92% for primary NSCLC compared with 44% for metastatic lesions with doses >20 Gy are given.(11) Additionally, series report a heterogeneous dose of radiation given, making direct comparisons by dose difficult. However, early reports of control do provide a basic framework from which to compare the efficacy of Nelfinavir with SBRT compared to those treated with higher doses of RT alone.

4.6 Rationale for Use in Liver Metastasis

The primary management of unresectable metastatic disease to the liver is systemic chemotherapy. Some uncontrolled trials have investigated liver-directed therapies such as transarterial embolization (TACE), radioembolization, stereotactic body radiation therapy (SBRT), chemoradiation (CRT), radiofrequency ablation, and cryotherapy in the palliative or, in rare cases, neoadjuvant setting(15, 24-27). Liver metastases are a common source of cancer morbidity and mortality and are often the only site of metastases. Major advancements in radiation treatment planning and delivery have resulted in resurgence in the use of radiation therapy (RT) as a treatment for liver tumors. With the development of 3-dimensional conformal radiation treatment (CRT), partial liver irradiation became possible. Stereotactic body radiation therapy (SBRT) is defined as highly focused, stereotactic localized, high-dose RT delivered in a hypofractionated course. In selected patients, very high local control rates have been observed, with minimal toxicity. Patients most likely to benefit from RT are those with liver confined disease, focal distribution of metastases, and metastases more than 1.5 cm from luminal gastrointestinal organs.

Chemotherapy and molecular-targeted agents rarely eradicate metastases permanently. For colorectal carcinoma liver metastases, selected resection series have yielded 5-year survival rates of approximately 50% showing that local therapy has the potential to cure “oligo” or isolated liver metastases (5, 9, 28-31). Patients are not suitable for resection because of medical or surgical reasons. The benefit of local therapy in non-colorectal liver metastases is less clearly defined, but long-term survival has been reported after the resection of liver metastases from sarcoma, breast cancer, and other tumor sites (32).

The dose-limiting toxicity from whole-liver RT is radiation-induced liver disease (classic RILD), initially called radiation hepatitis (33-35)and characterized pathologically by central vein occlusion as described by Reed and Cox.(36)With the advent of 3-dimensional

conformal radiation treatment (CRT) planning and delivery technology that allows for partial liver irradiation, and that higher tumor doses could be delivered safely as long as the mean dose to the liver was kept to less than safely tolerated whole-liver doses. At the University of Michigan, no cases of RILD after CRT for colorectal liver metastases were seen when the mean liver dose was <31 Gy in 1.5 Gy twice a day. This group also found the Lyman normal tissue complication probability model useful as a means of relating dose-volume histogram data to risk of liver toxicity (35). In recent years, the application of stereotactic body radiation therapy (SBRT) has allowed even more intensive tumor dose escalation in a hypofractionated schedule with increased conformality that limit the dose to the liver usually well below the threshold above which severe RILD is observed(15).

It is now recognized that some patients with "oligo," or few sites of metastases, may have isolated sites of metastases that can be potentially cured with local therapy. The term "oligometastases" was coined to refer to this stage of distant metastases. Typically, the entire burden of disease can be recognized as a finite number of discreet lesions. Although there is no strict definition of oligometastases, it is commonly interpreted to be no more than 5 or 6 metastatic sites. Milano et al. (9)from the University of Rochester have also shown that the net tumor burden for patients with 5 or fewer sites of macrometastatic disease, treated on 2 prospective SBRT protocols, was an independent predictor of overall outcome. Whether SBRT, as an adjunct to systemic therapy, to selected macroscopic metastases can influence overall survival by keeping the burden of disease below such a "lethal threshold" is being investigated.

Goodman et al.(15) reported a phase I dose-escalation single-fraction trial for patients with liver metastases or intrahepatic cholangiocarcinoma. Doses were escalated in 4-Gy cohorts from 18 Gy up to 30 Gy in 1 fraction. Twenty-six patients with 40 lesions were treated. There was no dose-limiting toxicity. The median follow-up was 17 months, and this corresponded to a 12-month local control rate of 77%. The 2-year actuarial survival rate was 50.4%.

Based on data above, in this study we will evaluate whether a Nelfinavir plus a single fraction of SBRT can be combined with Nelfinavir to control liver metastases with up to 5 liver metastases. Patients will be closely monitored for grade 3 or above liver toxicity including RILD.

4.7 Concurrent SBRT and Nelfinavir

The use of radiation therapy to treat metastatic tumors is well established and promising data are emerging with the use of SBRT for metastatic disease. However, the use of a single large fraction concurrent with a radiosensitizer as is being proposed is not of proven benefit. This investigation aims to confirm the safety and efficacy for SBRT used concurrently with a radiosensitizer in the setting of oligometastatic disease. The dose selected has been chosen with the belief that it is safe and effective based on prior experience with SBRT of lung cancer, pancreatic cancer and brain radiosurgery. All patients will be treated with a single fraction, targeted to the lesion concurrently with the radiosensitizer Nelfinavir.

On the basis of this preclinical evidence, we propose a phase I-II study of Nelfinavir combined with SBRT in patients with oligometastatic disease. Because the standard dose of Nelfinavir for HIV patients is known to be safe and does inhibit the phosphorylation of Akt and decrease tumor hypoxia, we propose to study this in conjunction with a 15 Gy dose of SBRT. Experience with single-fraction pulmonary and pancreas SBRT provides a useful dose for this trial. With published data establishing the relative safety of large single-fraction SBRT to the lungs and pancreas, we have decided to proceed to determine the safety of 15 Gy SBRT concurrently with the radiosensitizer Nelfinavir. Once this is established, we propose to continue to enroll more patients to the study at this dose to determine the efficacy of this type of therapy.

In general metastatic disease carries an extremely high mortality rate. Current therapies provide only partial palliation of symptoms and mild to moderate prolongation of survival. Patients are rarely cured of this disease; consequently, better treatment is clearly needed. The proposed treatment represents a logical extension of the current state-of-the-art radiation therapy. It has the potential to translate into more effective palliation and longer patient survival. Another advantage to the patient is that several weeks of radiation therapy can be accomplished in a single day, which is not inconsequential for patients with a limited life expectancy.

The proposed study represents an informed estimate based on current knowledge of SBRT doses and those administered in currently approved image-guided protocols (brain, base of skull, cervico-thoracic spine, pancreas and liver). This study will refine the current understanding of single fraction radiation tolerance for normal tissues, thereby making it possible to treat future patients more safely and aggressively.

5. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

All patients will be eligible to receive chemotherapy alone or conventional chemo-radiotherapy at the time of clinical or radiographic disease progression or at 4 weeks post-treatment.

5.1 Inclusion Criteria

5.1.1 Patient's tumor(s) to be treated is(are) ≤ 5.0 cm or ≤250 cm^3

5.1.2 Patient must have metastasis at one or more of the following sites: bone, liver, lymph node and/or lung. No more than five lesions will be treated.

5.1.3 Histological confirmation of malignancy (primary or metastatic tumor).

5.1.4 Patient may have any prior therapy allowed aside from having had prior radiotherapy to the treatment site (see exclusion criteria 5.2.3).

5.1.5 Patient must be ≥ 18 years of age.

5.1.6 Patient must have a life expectancy ≥ 9 months.

5.1.7 Patient must have an ECOG performance status ≤ 2.

5.1.8 Patient must have normal organ and marrow function as defined as:

Leukocytes	≥2,000/μL
Absolute Neutrophil Count	≥1,000/μL
Platelets	≥50,000/μL

5.1.9 Patient must have the ability to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

5.2.1 Patient has had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas, anti-angiogenic agents, or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

5.2.2 Patient receiving any other investigational agents.

5.2.3 Patient who has had any prior radiotherapy to the treatment site(s). As in, definitive therapy for lesion of interest. Field overlap from previous treatment is permitted at the discretion of the treating investigator.

5.2.4 Patient is taking concurrent drugs that are contraindicated with Nelfinavir, including any of the following:

Alfuzosin
Cisapride
Sildenafil (Revatio®)
Amiodarone
Quinidine
Rifampin
Dihydroergotamine

Ergonovine
Ergotamine
Methylergonovine
Hypericum perforatum (St. John's wort)
Lovastatin
Simvastatin
Pimozide
Midazolam
Triazolam
Oral Midazolam

5.2.5 Patient refuses to take a pregnancy test prior to treatment if the patient is a woman with child bearing potential.

5.2.6 Patient is participating in a concurrent treatment protocol.

5.2.7 Patient is a pregnant woman (pregnant women are excluded from this study because radiation treatment has known potential for teratogenic or abortifacient effects).

5.2.8 Patient refusesto sign informed consent.

5.2.9 Patient has poor liver function (>2.5 times normal of ALT/AST/Alk phos) suggestive of cirrhosis or steatohepatitis.

5.2.10 Patient has been treated with Nelfinavir within 3 months of entry into this trial.

5.2.11 Patient is receieving Warfarin (Coumadin).

6. TREATMENT PLAN

6.1 Diagnostic Procedures

A CT scan or MRI will be performed for tumor localization using rigid immobilization appropriate for stereotactic treatment. A separate PET-CT may be performed (all are optional) for diagnostic purposes and can be used for treatment planning with fusion -- this study would be done identically if the patient were having standard moderate dose radiation.

6.2 Therapeutic Procedures

Upon confirmation of eligibility and enrollment in the study, the following will be completed:

1) Demographics review, medical history and clinical exam
2) Review of concurrent medications
3) Vital signs, height and weight
4) CBC, chemistry panel and coagulation profile

5) Peripheral blood mononuclear cells will be collected and subsequently assayed for phospho-Akt before administration of Nelfinavir, on the day of SBRT, and optionally at the 1MFU.
6) CT or MRI of the involved site(s) (if not previously conducted within 1 month of start of Nelfinavir).
7) Positron Emission Tomography scan (optional) (if not previously conducted within 1 month of start of Nelfinavir).

Upon entry into the protocol, all patients will be seen by at least one of the Co-Investigator Radiation Oncologists. CT simulation will be performed with fabrication of a radiation therapy immobilization device (such as the Alpha Cradle) which will be custom made for each patient. The treating radiation oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed with a diagnostic radiologist on sequential axial computed tomography images. A radiosurgical treatment plan will be developed based on tumor geometry and location. The dose will be prescribed to the minimal isodose line that completely covers the GTV plus a 5 mm margin. Adjacent normal structures including but not limited to the heart, esophagus, aorta, spinal cord, kidneys, rectum, bowel, liver, and stomach within 5 cm of the GTV will be identified for the purpose of limiting incidental radiation to these structures.

In addition, prior to treatment delivery, a four-dimensional cone beam CT study will be performed on individual patients to assess respiration in these patients and to determine tumor targeting accuracy for those tumors that may be subject to respiratory motion such as those in the lung or liver. If tumor motion is greater than 5 mm, the planning target volume (PTV) will be expanded to account for respiration.

Within three weeks of the initial treatment planning imaging study, SBRT will be administered using image-guidance. An Alpha Cradle (or equivalent immobilization device) will be used to minimize movement of the chest, spine, and abdomen during treatment. During treatment, real time cone beam CT images of the patient's body site of interest will be obtained. Cone beam CT scan will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment cone beam CT, is within tolerance for the body site.

The patient will begin on 1250 mg oral Nelfinavir twice a day for seven days prior to starting SBRT. Once having completed the Nelfinavir, the patient will begin SBRT. Afterwards, the patient will again take Nelfinavir for 7 days. If scheduling or safety prevents all lesions from being irradiated within one day, participants will complete Cycle #2 of Nelfinavir then undergo a minimum of 7 days "clear out". Following this break participants will repeat Cycle #1 of Nelfinavir then receive radiation to the remaining lesions followed by a repeat Cycle #2 of Nelfinavir. This process may not exceed three "rounds" of treatment (NFV1, SBRT, NFV2) and may include repeat imaging and/or blood work.. This dose of Nelfinavir has been shown to reliably inhibit Akt phosphorylation.

Patients will be evaluated for adverse events/toxicities during their treatment.

6.2.1 The dose limits for surrounding critical structures are as follows:

- **Spinal Cord**: maximal allowable dose should be = 1000 cGy in 1 fraction
- **Lung**: 2/3 of the lung volume should be kept under 500 cGy.
- **Heart**: 50 % of the heart volume should be kept under 1000 cGy.
- **Esophagus**: 50 % of the esophagus volume should be kept under 1000 cGy and no single point dose in the esophagus should exceed 2000 cGy.
- **Brachial Plexus**: maximal allowable point dose = 1000 cGy
- **Liver**: One third of the uninvolved liver or approximately 700 cc <15 Gy.
- **Kidneys:** 75% of volume of each kidney <5 Gy.
- **Small Bowel:** <5% of bowel limited to <20 Gy.

6.3 Follow-Up Procedures

Subsequent to SBRT, patients will be followed clinically for toxicity and interval history at Months 1, 2, 3 6, 12, and every 6 months thereafter until 3 years post SBRT. A detailed medical and physical examination will be performed at 4 weeks, 3 months, 6 months and 1 year post SBRT. The following procedures are optional at Months 1, 3, 6 and every 6 months through 3 years post SBRT:

- A complete blood count (CBC) and comprehensive chemistry panel
- CT scan or MRI including the treated site (Note: this is required at Months 3 and 6 for the reason noted below)
- Physicial Exam and ECOG Performance Status

PET-CT will be recommended at 3 months, 6 months, and annually thereafter however all are optional.

CT scans at 3 and 6 months will be used to determine radiographic response based on RECIST 1.1 criteria.

All follow-ups may be conducted by telephone for patient convenience. Study staff will request any of the optional procedures noted above that were performed by local phsicians to be forwarded for study records.

6.4 Duration of Therapy

The patient will initiate Nelfinavir oral therapy twice daily seven days prior to SBRT. Within three weeks of the initial treatment planning imaging study, SBRT will be administered in a single dose to each treated lesion. After completion of SBRT a second seven day cycle of Nelfinavir will occur.

If scheduling or safety prevents all lesions from being irradiated within one day, participants will complete Cycle #2 of Nelfinavir then undergo a minimum of 7 days “clear out”. Following this break participants will repeat Cycle #1 of Nelfinavir then receive radiation to the remaining lesions followed by a repeat Cycle #2 of Nelfinavir. This process

may not exceed three "rounds" of treatment (NFV1, SBRT, NFV2) and may include repeat imaging and/or blood work..

6.5 Duration of Follow-Up

It is anticipated that this study will last 3 years.

6.6 Criteria for Patient Removal

Unacceptable adverse events grade IV or greater with an attribution of possibly related while on Nelfinavir before SBRT.

6.7 Alternatives

The study has been designed (see above) to minimize potential risks to participants. This is primarily through designation of a dose shown to be safe in previous SBRT trials and careful patient monitoring. The risk of Nelfinavir is minimal as has been documented for greater than a decade following FDA approval in post-market surveillance. Risks to confidentiality will be minimized by having access to study records avaialble only to the investigators with the exception of the standard clinical records (lab values, dictations, operative notes, etc) which are maintained through the Weinberg Comprehensive Cancer Center.

Standard therapies for metastatic disease include conventional radiotherapy, chemotherapy, or observation. Such treatment may or may not be applicable for patients enrolled in this study. Regardless, patients will be expected to forgo standard chemotherapy or radiotherapy until there is evidence of clinical or radiographic disease progression or until completion of a 4-week post-treatment evaluation.

The amount of radiation administered via protocol therapy will be considered in determining how much additional radiation can be given using conventional external beam fractionation.

6.8 Costs

Patients and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol except the study drug nelfinavir. Nelfinavir will be supplied to the participant at no cost.

6.9 Compensation

Patients and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol.

6.10 Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up.
- Study is terminated for any reason.

If participants withdraw from the study, they will be followed for survival data.

7. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

7.1 Investigational Agent

Nelfinavir is the commercially available agent being used in this study.

7.2 Availability

Nelfinavir will be ordered and obtained from the Johns Hopkins Pharmacy.

7.3 Agent Accountability

Only subjects enrolled in the study may receive Nelfinavir, in accordance with all applicable regulatory requirements. Subjects enrolled on the study will self-administer nelfinavir and keep track of their dosing intake via a study drug administration record. Nelfinavir will only be dispensed to the patient when the treating physician involved in the study provided a written order.

8. DOSING DELAYS/DOSE MODIFICATIONS

There will be no dose modifications.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Assessment of Phospho-Akt

9.1.1 A blood sample (plasma and serum) will be obtained by venipuncture into a vacutainer coated with 3.2% sodium citrate anticoagulant before Nelfinavir administration, on the day of SBRT treatment, and optionally at the 1MFU. The samples will be centrifuged within 30 minutes of collection and processed in preparation for phosphor-akt assay then stored at -80°C for future analysis.

9.1.2 The study coordinator will transport the specimen to the laboratory of Phuoc T. Tran, M.D., PhD for storage and processing.

9.1.3 Specimen will be labeled by patient case ID to protect patient privacy

10. STUDY CALENDAR

Parameter	Pre-Study	NFV^ Cycle #1	SBRT ~	NFV^ Cycle #2	Follow-Up%								
					1M (+/- 5 days)	2M (+/- 7 days)	3M[i] (+/- 7 days)	6M@, h, i	12M@,i	18M@,i	24M@,i	30M@,i	36M@,i
Informed Consent	X												
Demographics	X												
Med HX & Medication Rev	X				X		X	X	X	X	X	X	X
Physical Exam	X				X		X	X	X	X	X	X	X
Vital Signs	X				X								
Height	X				X								
Weight	X				X								
Perf Status	X		X		X	X	X	X	X	X	X	X	X
CBC w/ Diff[a]	X[f]				X		X	X	X	X	X	X	X
Serum Chem[b]	X[f]				X		X	X	X	X	X	X	X
Coagulation Profile	X[f]												
Blood Draw for Phospho-Akt	X[f]		X		X*								
CT or MRI[h] (of Involved Site(s)[c])	X[f]				X		X	X	X	X	X	X	X
PET-CT*	X[f]						X	X		X		X	
CT-Guided Fiducial Placement*	X												
AE Evaluation[g]	X	X[d]		X[d]	X	X	X	X	X	X	X	X	X
B-HCG[e]	X												

^ *Nelfinavir (NFV):* to be administered in two cycles (1250 mg BID (orally) for 7 days/cycle). Cycle #1 will conclude the day prior to SBRT. Cycle #2 will initiate the day after completion of SBRT.
~ *SBRT:* to be administered in one day. However, if scheduling or safety prevents all lesions from being irradiated within one day, participants will complete Cycle #2 of Nelfinavir then undergo a minimum of 7 days "clear out". Following this break participants will repeat Cycle #1 of Nelfinavir then receive radiation to the remaining lesions followed by a repeat Cycle #2 of Nelfinavir. This process may not exceed three "rounds" of treatment (NFV1, SBRT, NFV2) and may include repeat imaging and/or blood work. Accordingly, the study calendar will be affected.
% Follow-up appointments will be scheduled based on date of SBRT completion.
* indicates optional
@ +/- 30 days
a. Including platelets.
b. Albumin, Alkaline Phosphatase, Total Bilirubin, Bicarbonate, BUN, Calcium, Chloride, Creatinine, Glucose, Potassium, Total Protein, SGOT [AST], SPGT [ALT], Sodium.
c. Tumor measurements are to be calculated after all radiographic tests.
d. Will occur on the last day of Nelfinavir Cycle #1 or on date of SBRT administration and the last day of Nelfinavir Cycle #2. May be conducted via phone.
e. Serum pregnancy test (women of childbearing potential).
f. Should occur within 30 days of start of Nelfinavir.

g. Follow up AE evaluations may be conducted via phone.
h. Required at 3 and 6 months
i. May be conducted via telephone. All procedures are optional, EXCEPT for interval history and AE evaluations. Study staff will remind subjects of upcoming optional procedures at each telephone or follow-up visit. If obtained locally, staff will request that the results be forwarded for study records.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect-Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 4 weeks after the initial treatment, 12 weeks after treatment, 24 weeks after treatment, and every 24 weeks thereafter.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee (30). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.2 Definitions

Evaluable Population: will consist of all patients who have received 28 doses of Nelfinavir treatment preceding SBRT.

Safety Population: Will consist of all subjects who were enrolled and have taken at least one dose of the study medication. This will be used to assess the clinical safety and tolerability of the study.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have completed all fractions of SBRT, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.3 Disease Parameters

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with diagnostic techniques (CT, PET/CT (all are optional), or MRI). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Target Lesions: Target lesions in this study will be considered oligometastatic sites up to a maximum of 5 lesions per patient. They should be recorded and measured at baseline. Target lesions should be equal to or larger than 10 mm in the smallest cross-sectional diameter on CT or MRI and/or any lesion that shows increase metabolic uptake on PET/CT scans. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-Target Lesions: N/A

11.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Conventional CT, PET/CT (all are optional), and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

11.5 Response Criteria (via RECIST 1.1)

11.5.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

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

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

11.5.2 Evaluation of Non-Target Lesions

N/A

11.5.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Best overall response will be based on the overall response of the target lesions.

11.5.4 Duration of Response

Response will be defined as evidence of CR, PR, or stable disease. The duration of response will be measured from the start of treatment until the criteria for progression are met.

Duration of CR or PR: The duration of CR or PR will be recorded from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that current or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.5.5 Clinical Response Parameters

Time to Local Progression (TTLP) is defined as the elapsed time from the start of treatment to the date of documented local progression or death, whichever happens earliest.

Progression-Free Survival (PFS) is defined is the time from starting treatment to the time of first documented tumor progression or death due to any cause, whichever occurs first. Death is considered as an event here. For subjects whose disease does not progress or who do not die, PFS will be censored at the time of the last visit.

Time to Progression (TTP) is defined as the time from starting treatment to the time of first documented tumor progression. Subjects who do not progress will be censored at the time of the last contact. In addition, death from any cause will also be censored.

Overall Survival (OS) is defined as the time from starting treatment until death due to any cause. For subjects who do not die, time to death will be censored at the time of last contact.

Locoregional Control (LRC) is defined as the time from starting treatment until local and/or regional relapse is documented

11.5.6 Response Review

All responses will be reviewed by the study co-investigator radiologist.

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12.2 Definitions

12.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

12.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

12.2.3 Expectedness

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

12.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned 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 is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

12.3 Potential Adverse Events

Signs and symptoms of disease progression are not considered AEs. The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

Because patients are receiving standard treatments, which are not part of this study, their treating physician will be counseling them on the risk of their treatments, including the risk of surgery, radiation therapy, and/or chemotherapy, whichever is appropriate for the type and the stage of their cancer. The procedures related to the study are phlebotomy, PET imaging (all are optional), SBRT, and Nelfinavir administration.

Phlebotomy can cause pain, bleeding, and rare needle site infection. PET imaging results in low dose radiation exposure (see Investigator's Brochure for details of dosimetry), which has an extremely small risk of causing a secondary cancer.

12.4 Stereotactic Body Radiation Treatment

It is difficult at this time to predict with confidence the complication rate from the proposed SBRT; however, it is reasonable to extrapolate from the current experience with SBRT to the lung and pancreas. One significant toxicity is radiation pneumonitis, which can be manifested as fever, increased excertional dypsnea, pleuritic chest pain, and peritumoral infiltrate on chest imaging. It generally occurs between 1 to 3 months of completion of radiotherapy. The risk of grade 2-4 radiation pneumonitis is aproximately 10-15% in patients treated with standard fractionated large field radiotherapy and higher in patients treated with combined chemoradiotherapy. It is highly dependent on the volume of the lung treated to high dose and the mean lung dose. At this point, the incidence of RT pneumonitis from stereotactic radiosurgery for small pulmonary tumors is unknown. However, if the treated tumor volume is kept $\leq$ 65 cc, the risk should be < 10-15% with the proposed dose level.

Other toxicities commonly associated with such treatment includes dysphagia, odynophagia, nausea, vomiting, anorexia, and weight loss. Some of these symptoms can also be due to tumor progression. Clinical and radiographic assessments will be performed as indicated to identify all adverse effects, ascertain their etiology, and provide the most appropriate palliative measures. Complications orther than radiation pneumonitis, if any, will be graded according to the Common Toxicity Criteria, National Cancer Institute, version 4.0.

12.5 Nelfinavir

12.5.1 The safety of VIRACEPT (Nelfinavir mesylate) was studied in over 5000 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving VIRACEPT was diarrhea, which was generally of mild to moderate intensity. The frequency of Nelfinavir-associated diarrha may be increased in patients receiving the 625 mg tablet because of the increased bioavailability of this formulation.

Adverse events occurring in patients receiving VIRACEPT in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below:
Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain, and redistribution/accumulation of body fat.
Digestive System: anorexia, nausea dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.
Hemic/Lymphatic System: anemia, neutropenia, leukopenia and thrombocytopenia.
Metabolic/Nutritional System: increases in alkaline phosphatase, amylase, creatinine, phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, new onset or exacerbation of diabetes mellitus, dehydration, hepatitis, jaundice, and liver function tests abnormal.
Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.
Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.
Respiratory System: dyspnea, pharyngitis, rhinitis, and sinusitis.
Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.
Special Senses: acute iritis and eye disorder.
Urogenital System: kidney calculus, sexual dysfunction and urine abnormality.

12.5.2 The following additional adverse experiences have been reported from post marketing surveillance as at least possibly related or of unknown relationship to VIRACEPT:

Body as a Whole: hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever and edema).

Cardiovascular System: QTc prolongation, torsades de pointes.
Digestive System: jaundice.
Metabolic/Nutritional System: bilirubinemia, metabolic acidosis.

12.5.3 Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for overdose with VIRACEPT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since Nelfinavir is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

12.6 Fiducial Implantation

The risk associated with implantation of fiducials is primarily related to the small risk of pneumothorax associated with percutaneous placement of a needle within the lung. The procedure is analogous to percutaneous needle biopsy, a commonly performed procedure which is associated with a pneumothorax risk ranging from 16-40%. Of patients who develop a pneumothorax, most are managed by observation alone, with only 5-7% of patients requiring intervention such as chest tube placement. Another rare risk of fiducial placement is exacerbation of chronic obstructive lung disease, which may require medical interventions, including rare hospitalization. Other potential complications of fiducial implantation is embolization. In the literature, there is little data regarding this potential complication, but if one were to extrapolate from patients suffering gun-shot wounds to the chest, either with pellets or bullets, standard surgical teaching is not to removal of the small foreign bodies as they rarely cause harm. To further avoid the potential risk of embolization, every effort will be made to place the fiducials in the substance of te tumor rather than in the adjacent lung parenchyma. Theoretically, fiducials implanted elsewhere in the body could embolize to the lungs; to date this has not been reported.

12.7 Reporting Procedures

12.7.1 General

Adverse events will be recorded at each visit. If an adverse event requiring medical attention occurs between visits, this will be recorded as well. The variables to be recorded for each adverse event include, but are not limited to, onset, resolution, intensity, action taken, outcome, causality rating and whether it constitutes an SAE or not. The intensity of the adverse event should be captured using CTCAE criteria, version 4.0, when possible.

Pregnancy should be excluded before enrollment. Pregnancy in itself is not reported as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

12.7.2 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

13. DATA AND SAFETY MONITORING PLAN

This is a DSMP Level I study under the SKCCC Monitoring Plan (see Appendix II). A Level I study requires both internal and external data monitoring. The Principal Investigator is responsible for internal monitoring for both safety and data quality. External data monitoring will be performed by the SKCCC at Johns Hopkins Clinical Research Office Quality Assurance Program (CRO QA).

Data and safety monitoring oversight will be conducted by the SKCCC at Johns Hopkins Safety Monitoring Committee. Per the SKCCC at Johns Hopkins Safety Monitoring plan, the CRO AQ will forward summaries of all monitoring reports to the Safety Monitoring Committee for review. All reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB will also be reviewed by the Safety Monitoring Committee Chair (or designee) and QA manager.

14. REGULATORY CONSIDERATIONS

14.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB prior to implementation.

14.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction

with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

14.3 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15. STATISTICAL CONSIDERATIONS

15.1 Endpoints

15.1.1 Primary Objective

To determine the 6-month freedom from local progression of the radiosensitizer Nelfinavir used concurrently with 15 Gy of stereotactic body radiation therapy (SBRT) delivered in 1 fraction (per lesion site) in patients with oligometastatic disease.

15.1.2 Secondary Objectives

- To describe the toxicity of SBRT combined with Nelfinavir delivered for the population enrolled using grading with CTCAE v. 4.0
- To determine the local control at 6 months after SBRT is delivered to a dose of 15 Gy in 1 fraction (per lesion rate) combined with Nelfinavir in patients with oligometastatic disease.
- To assess long-term clinical outcomes of this patient population after completion of SBRT and Nelfinavir by measuring progression-free survival and overall survival. Progression-free survival will be measured from time of enrollment to date of disease progression or death. Patients who are lost to follow-up will be censored for determination of progression-free survival on the date of their last evaluation. Overall survival is defined as time from enrollment to death due to any cause.
- To assess quality of life following completion of SBRT and Nelfinavir using pre- and post-SBRT completion of the Brief Pain Inventory form which will be filled out by the patient at the treatment response intervals outlined above.

15.2 Sample Size/Accrual Rate

The primary endpoint will be freedom from local progression at 6 months. The treatment regimen would be considered of insufficient activity for further study in this population

if the 6-month FFLP rate is 70% or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 90% FFLP at 6 months. The accrual rate is 3 patients per month, and the patients will be followed for up to 3 years. A total of 42 patients will be entered in the study accounting for a 15% dropout rate. This study would have 90% power to detect an improved 6-month FFLP from 70% to 90% using a two-sided test at significance level 0.05. Alternatively, this corresponds to the power to detect a reduction of hazard rate from 0.06 to 0.02, a reduction of 70% in hazard rate.

There will be no interim analysis for futility, since the progression endpoint will not have been reached by a meaningful number of patients before full accrual.

15.3 Safety Run-In Phase

There is no previous experience with SBRT used concurrently with Nelfinavir in this study population. Therefore, to ensure that the combination is safe, the first six patients will be treated and observed for toxicity for 30 days after radiation before continuing with further accrual. 6 patients will be enrolled at the proposed dose of Nelfinavir and SBRT.If ≤ 2 toxicity events occur in the first 6 patients within 30 days of therapy, we proceed with additional accrual with this regimen to complete a total of 42 patients. If ≥ 3 toxicity events occur among the first 6 patients, we will suspend the study pending data review.

Toxicity Event: ≥grade 3 adverse event (CTCAE v 4.0) with an attribution of possible, probable, or definite.

15.4 Early Stopping Guidelines:

This study will monitor site-specific grade 4/5 toxicity. If it becomes evident that the proportion of grade 4/5 toxicity at specific sites convincingly exceeds 20%, the study will be halted for a safety consultation. Specifically, we will apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of toxicity being larger than 20% threshold is 75% or higher. The monitoring rule uses Beta (0.5, 5.5) as prior distribution. This means that our prior guess of the proportion of toxicity is 8.3%, and there is 90% chance that this proportion is 0.04%-30.6%. The monitoring will start from the 7th patient, and the decision rule for safety stopping is as follows:

Stop if:

# grade 4/5 toxicities ≥	4	5	6	7	8	9	10
Out of # patients	7 - 10	11 - 14	15 - 18	19 - 23	24 - 27	28 - 32	33 - 36
# grade 4/5 toxicities ≥	11	12					
Out of # patients	37 - 41	42					

The operating characteristics of the stopping rule are shown below and are based on 5000 simulations:

True AE rate	% simulated trials declaring unsafe	Average sample size (out of 42)
0.10	2.1	41.4
0.15	11.3	39.2
0.2	32.7	34.3
0.25	59.5	27.7
0.3	81.9	21.2
0.35	93.6	16.1
0.4	98.3	12.7

15.5 Analysis of Primary Objective

The primary efficacy analysis will estimate 6-month freedom from local. Freedom from local progression (FFLP) is defined as the elapsed time from the start date of treatment to the date of documented local. Patients who die without local progression will be censored at the time of death. We will plot the Kaplan-Meier curve for FFLP and estimate 6-month FFLP and its 95% confidence interval based on KM estimate and Greenwood's formula. The analysis population includes all registered subjects who have received at least one fraction of SBRT. Patients that develop distant metastasis before local progression will remain on study.

15.6 Analysis of Secondary Objectives

- For safety analysis, adverse events will be summarized by type and grade.
- Hazard rate estimates and 95% confidence intervals as well as Kaplan-Meier (KM) estimates will be used to summarize survival (OS), progression free survival (PFS), time to locoregional progression (TTLP) and time to distant progression (TTDP), duration of response functions over time. The median OS, PFS, TTLP and TTDP will be reported.
- The efficacy of SBRT combined with Nelfinavir with oligometastatic disease will also be determined by measuring local control of each lesion at 6 month. Each metastatic lesion will be considered a target lesion and independently evaluated for response using RECIST 1.1. The lesion will be coded as being locally controlled if it is considered stable radiographic disease or if there is evidence of a partial or complete response. Local control assessment will start at one month following completion of protocol treatment and continuous assessment will be pursued during the follow-up period. The proportion of the lesions that have a stable or better response will be estimated using generalized estimating equation. The above analyses will also be performed by metastases site (bone, liver and lung).
- Quality of life will be assessed using the Brief Pain Inventory form. An overall score will be calculated pre-treatment and at the time of the 2nd radiologic reassessment. The change in score will be evaluated with a paired t-test.
- The analysis for the correlative study will be done by Western blot. The change of phospho-Akt levels will be correlated to progression-free survival outcome.

15.7 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment for SBRT.

15.8 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression).

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The reason for performing subset analyses would be to generate hypotheses for future prospective clinical trials.

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APPENDIX I: Brief Pain Inventory Form

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

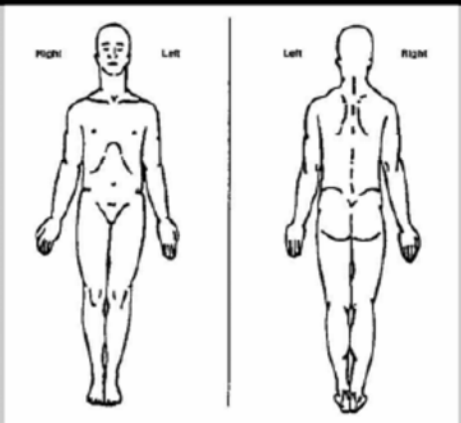
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

APPENDIX II: SKCCC DSMP

APPENDIX III: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.