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**TITLE:** A Phase II Trial of Integrating Stereotactic Body Radiation Therapy with Selective Targeted Therapy in Stage IV Oncogene-driven Non-Small Cell Lung Cancer

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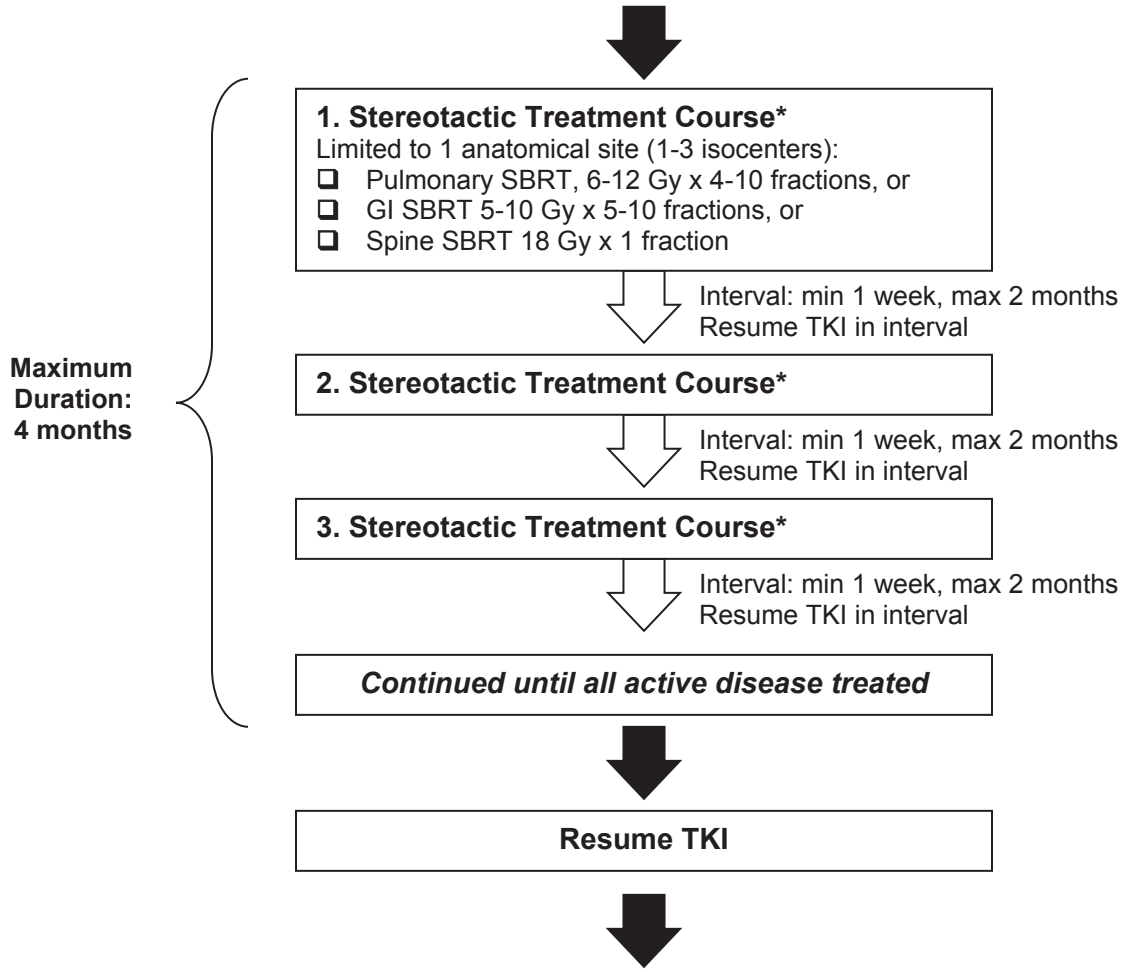
## SCHEMA

### Phase II trial of integrating SBRT into the management of stage IV oncogene-driven NSCLC

**Stage IV Oncogene-driven NSCLC**
- ❑ On selective TKI, within 6-12 months of starting TKI, depending on specific drug
- ❑ Residual disease on TKI limited to:
  PULM – primary or/and 1-2 metastases (max 5 cm each), and/or
  GI – 1-4 liver metastases (max 5 cm each) or/and 1-2 adrenal metastases (max 4 cm each), and/or
  Spine – 1-2 spine metastases (1-3 vertebral bodies each), and/or
  CNS – up to 4 brain metastases, max size 3 cm *




**Frequency of patients with distant failures (in new sites) as first site of failure at 12 months**

* Recommended maximum number of metastatic target lesions outside the brain is 5. Any new brain metastases will be treated with stereotactic radiosurgery (SRS) as part of standard-of-care therapy, which is not part of protocol treatment

** TKI will be held on days of SBRT. TKI is part of standard-of-care therapy, which is not part of protocol treatment.

CNS, central nervous system; GI, gastrointestinal; NSCLC, non-small cell lung cancer; PULM, pulmonary; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor

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# 1. OBJECTIVES

## 1.1 Study Design

Stereotactic body radiation therapy (SBRT) is an advanced radiation therapy modality that involves the delivery of ablative individual doses of radiation to tumors in various extracranial sites with high precision and in a shorter amount of time than with traditional radiation. The precision used in SBRT minimizes the radiation dose received by a volume of the normal surrounding organs and tissues, thus limiting radiation toxicity (1-4).

SBRT has emerged as a standard therapy for medically inoperable patients with peripherally located stage I non-small cell lung cancer (NSCLC) (5-9). Recently, a number of studies have explored the benefits of metastasis-directed SBRT in low metastatic burden or oligometastatic stage IV NSCLC. These studies have shown that SBRT can achieve high rates of local control of treated lesion (typically 70-90%) in patients with limited pulmonary, hepatic, adrenal, and spinal metastases (4-7, 10-26). It has been hypothesized that maximum cytoreduction through local control of metastases will result in longer progression free survival (PFS) and better outcomes in patients with low burden metastatic NSCLC (14).

Oncogene-driven cancers represent a unique subset of NSCLC that responds well to targeted tyrosine kinase inhibitors (TKI) (27). These include NSCLC with activating mutations in the epidermal growth factor recetor (EGFR) and EML4-ALK or ROS1 translocations. The initial TKI response is typically associated with a prolonged PFS in oncogene-driven cancers (7-13 months) compared to the general population of NSCLC, and is better than expected with conventional chemotherapy (~3-4 months) (28-32). Recent data demonstrate even longer median PFS times for newer TKIs, such as ~18 months for first-line osimertinib used against EGFR-mutant NSCLC (32a), and a range of PFS times for different ALK-directed TKIs, with at least ~18-20 months for first-line alectinib (32b,c). Oncogene-driven NSCLC therefore represents a potentially ideal patient population for consolidative SBRT as TKI are effective in eliminating micrometastatic disease, and may convert patients whose disease extent is too large at diagnosis to candidates with low metastatic burden that could be targeted with SBRT. Furthermore, consolidative SBRT to residual metastases following TKI therapy may eradicate cell clones with acquired TKI resistance which is a major clinical challenge in the management of this patient population (33-36).

Therefore, SBRT to residual sites of originally present cancer (“original sites”) will not only decrease the frequency of failure in these sites, but it also hypothesized to decrease the probability of hematogenous spread from persistent original disease to anatomical sites that were not originally involved by cancer (“distant sites”) . However, despite the overall theoretical benefits of SBRT in stage IV NSCLC, there are no published prospective clinical trials of SBRT for stage IV NSCLC, and more specifically in patients with oncogene-driven NSCLC (14-16).

SBRT can be delivered using either photons or protons. The main benefit of protons over photons is the absence of exit dose and avoidance of a low-dose bath in the patient. This

offers the opportunity for highly conformal (i.e., precise) dose distributions while simultaneously irradiating less normal tissue (37-39). High dose conformality is achieved through the use of a lower number of beams (2-3) compared to photon-based SBRT (~6-11), which leads to a reduction of the integral dose of radiation delivered to patients (39). In a setting where multiple metastatic sites are to be treated, the use of proton SBRT may therefore be advantageous (37-39).

We hypothesize that an SBRT regimen that integrates proton radiation for treatment of sites of residual disease following initiation of targeted TKI treatment will decrease the frequency of distant failures as first site of failure in stage IV oncogene-driven NSCLC patients from 40% to 20% by 1 year post-SBRT. To test this hypothesis, we propose to conduct a phase II prospective study of 30 patients to investigate the benefits as well as safety of consolidative SBRT in the management of low metastatic burden stage IV oncogene-driven NSCLC.

## 1.2 Primary Objectives

To determine the 12-month frequency of patients with distant failures as first site of failure associated with a treatment regimen of a targeted TKI and consolidative SBRT in patients with stage IV oncogene-driven NSCLC.

## 1.3 Secondary Objectives

1) To describe toxicities of treatment using CTCAE v4.0
2) To determine median PFS time
3) To analyze the pattern of original and distant site failures
4) To determine 2-year local control rate of irradiated lesions
5) To determine median overall survival time and 2-year overall survival

## 2. BACKGROUND

### 2.1 Study Agent(s)

Proton Beam Radiation

There have been unprecedented efforts in radiation oncology to develop sophisticated, conformal techniques in order to improve the outcome for cancer patients. The aim of these new techniques is to concentrate the radiation dose distribution more completely on the disease target, thereby sparing critical normal tissues and increasing the target dose. To this end, there are an increasing number of centers in the United States seeking to take advantage of the superior physical characteristics of proton beam radiation.

The basis for the advantages of proton beam radiation lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different (Figure 1A).

Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed

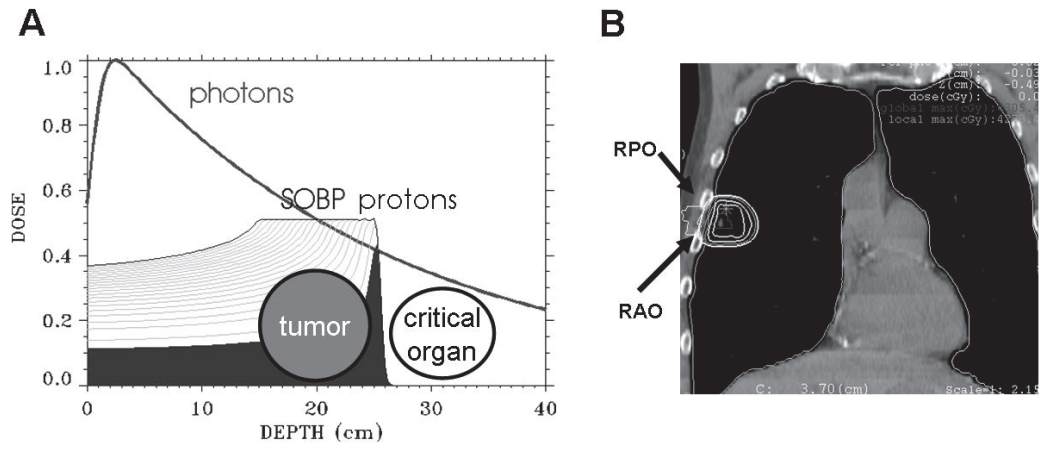


Fig. 1. Illustration of the therapeutic advantages of proton beam radiation. (A) Depth dose characteristics of a single proton portal versus a photon beam. Note the lack of exit dose with protons allowing sparing of distal normal tissue structures. The proton Bragg peak is spread out (SOBP), so that the entire tumor is encompassed by the desired dose. (B) Isodose distributions for a 70 year-old man with extremely poor lung function and oxygen dependence of 6 L NC. The 1.5 cm lung cancer was encompassed by two right anterior oblique (RAO) and posterior oblique (RPO) beams. Only 5% of the right lung was exposed to a dose of 20 Gy or more while the left lung received zero dose.

dose (energy absorbed per unit mass) - known as the Bragg peak. In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40% of the maximum dose. The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated - several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peak" (SOBP) (39).

The main benefit of proton therapy over photon beam radiotherapy is the absence of exit dose, which offers the opportunity for highly conformal (i.e., precise) dose distributions, while simultaneously irradiating less normal tissue. This technology therefore reduces irradiation to normal tissue, while permitting dose escalation to levels not achievable with standard techniques (39). Of note, high dose conformality can be commonly achieved through the use of only 2-3 protons beams, compared to multiple beams required for photon-based radiation therapy, which leads to a reduction of radiation exposure to healthy normal tissues. This principle is illustrated in Figure 1B, in which the use of 2 proton beams achieved high precision dose delivery to a small peripheral lung tumor while achieving maximum lung sparing in a patient with extremely poor lung function. Due to their evident superiority, protons are being increasingly used in a variety of disease sites with excellent clinical outcomes reported to date (reviewed in (39)).

Stereotactic Body Radiation Therapy

*Early-Stage NSCLC*

In recent years, stereotactic body radiation therapy (SBRT) has emerged as a highly promising treatment for medically inoperable patients with early-stage NSCLC (reviewed in (5, 7-9, 17, 40-45)). SBRT is a specialized type of radiation therapy that pinpoints high “ablative” doses of radiation directly on the cancer in a shorter amount of time than traditional radiation. Typically 45-60 Gy are delivered at 10-18 Gy per fraction, thus needing only 3-5 fractions distributed over 1-2 weeks. The delivery of large dose fractions is the major feature that separates SBRT from conventional radiation treatment. In order to minimize normal tissue toxicity, conformation of high doses to the tumor target and rapid fall-off of doses away from the target is critical. The practice of SBRT, therefore, requires a high level of confidence in the accuracy of the entire treatment delivery process. In SBRT, confidence in this accuracy is accomplished by the integration of modern imaging, simulation, treatment planning, and delivery technologies into all phases of the treatment process (2, 7, 43, 46). Reported treatment outcomes have been excellent, with 3-year local failure rates of ~10%, regional failure rates of < 10%, cause-specific survival rates of > 80%, and overall survival rates at 3 years of > 50% (3, 5, 6, 17, 44).

*Stage IV Cancer*

A number of studies have been conducted to explore the benefits of using SBRT in the treatment of metastatic disease (11, 12, 15, 16, 18-26, 47-49). Published studies of metastasis-directed SBRT can be divided into three types. First, studies in which various types of primary tumors or a range of metastatic locations are treated. Second, studies in which a single metastatic site is treated, such as the lungs or liver. Third, studies in which investigators focus on one histological type. To date, phase I and II data have been published for hepatic, pulmonary, spinal, adrenal and multiple-organ metastatic sites (11-13, 15, 16, 18-26, 49). Tables 1 and 2 show an overview of published case series in patients with oligometastases (defined for the purpose of this study as 1-5 metastases) (15, 16, 21, 22, 25, 26, 49-66). Although the studies reviewed are heterogeneous in terms of site, primary histology, and dose, control rates for treated metastases are generally around 80%.

At present, there exist no standardized SBRT techniques and dosing schemes for patients with metastatic disease. This is because metastases vary in volume, location within an organ and proximity to surrounding organs that have various tolerances to radiotherapy. Most studies published to date using various radiation dosing schemes have resulted in high rates of tumor control across many different organs (Tables 1 and 2). Even large-volume metastases (>5 cm diameter) have been shown to be well-controlled using SBRT with minimal toxicity (11, 12, 18, 22, 44). A study of patients with large-volume metastases treated with SBRT found that 50 Gy in 5 Gy fractions or three fractions of 12–16 Gy could be delivered safely and effectively with 87% treated-metastasis control (67). Taken together, the results of SBRT for multiple-organ metastases are similar to those reporting on surgical removal of single-organ metastases. However, unlike patients selected for surgical metastatectomy, these series include patients medically unfit for surgery or patients who have technically unresectable tumors. Thus, these data include patient populations previously unable to receive effective metastasis-directed therapy (68).

*Pulmonary and Hepatic Metastases*

The lung is the most widely studied organ for the delivery of SBRT to metastases because the imaging characteristics of pulmonary metastases enable direct targeting via integrated imaging on radiotherapy devices or indirect targeting with fiducial markers. Both prospective single-dose and dose-escalation studies have demonstrated high rates of treated-metastasis control (89–96%) with promising 2−year survival rates (38–39%, Table 1) (15, 16, 21, 49-52). Another commonly investigated target organ for SBRT for metastases is the liver. SBRT for hepatic metastases is a challenging process for radiotherapy planning and delivery because defining the anatomical extent of the metastases often requires diagnostic MRI fusion and incorporation of respiratory motion management techniques (18, 21, 69, 70). Phase I and II studies based on fixed doses, dose escalation and normal tissue complication probabilities have demonstrated high rates of treated-metastasis control (71–92%) as shown in Table 1. The long-term liver function remains normal in treated patients without hepatic insufficiency prior to SBRT, as long as standard radiation dose constraints are observed (16, 18, 21, 70).

*Spinal Metastases*

To date, phase I and II studies for spinal SRS and multi-fraction SBRT have demonstrated favorable treated-metastasis control rates (86–90%) for patients without spinal-cord compression (Table 1). Doses varied but in most studies were delivered in one to five fractions, often 16–20 Gy in one fraction or 27 Gy in three fractions. Similar to intracranial SRS, spine SBRT has been shown to be effective in the retreatment of metastases that progress following fractionated radiation therapy. In addition, SBRT has been shown to be very effective in palliating pain associated with spinal metastases (53-55).

Table 1: Selected series of extracranial SBRT for metastases in specific organs

| *Study* | *# Metastases Treated* | *#Metastases Treated per Patient (range)* | *SBRT Dose Fractionation* | *Control Rates for Treated Metastases (%)* | *Overall Survival (%)* |
|---|---|---|---|---|---|
| ***Lung Metastasis*** | | | | | |
| *Rusthoven et al. (15) multicentre (n = 38)* | 63 | 2 (1–5) | 48–60 Gy in 3 fractions | 2-year: 96 | 2-year: 39 |
| *Wulf et al. (50) single centre (n = 41)* | 92 | 1 (1–2) | 12–30 Gy in a single fraction | 1-year: 89 | 1-year: 84 |
| *Okunieff et al. (26) single centre (n = 30)* | 125 | 2.6 (1–5) | 50–55 Gy in 10 fractions | 3-year: 91 | 2-year: 38 |
| *Inoue* et al. (49) *single centre (n=22)* | 31 | 1(1-2) | 48 Gy in 4 fractions | NR | 3-year: 72 |
| *Takahashi* et al. (51) *single centre (n=42)* | 52 | 1 (1-2) | 20-56Gy in 1-6 fractions | 2-year: 87 | 2-year: 65 |
| ***Liver Metastasis*** | | | | | |
| *Rusthoven et al. (16) multicentre (n = 47)* | 63 | 1 (1–3) | 36–60 Gy in 3 fractions | 2-year: 92 | 2-year: 30 |
| *Katz et al. (21) single centre (n = 69)* | 174 | 2.5 (1–6) | 50 Gy in 10 fractions | 1-year: 76 | 14-month: 50 |
| *Lee et al. (52) single centre (n = 68)* | 143 | 1 (1–8) | Based on normal tissue complication probability (6 fractions) | 1-year: 71 | 1.5-year: 47 |
| ***Spine Metastasis*** | | | | | |
| *Wang et al. (53) single centre (n = 149)* | 166 | 1 | 27–30 Gy 3 fractions | 1-year: 86 | 1-year: 68.5 |
| *Yamada et al. (54) single centre (n = 93)* | 103 | 1 | 18–24 Gy 1 fraction | 15 month: 90 | 45-month: 36 |
| *Gibbs et al. (55) single centre (n = 74)* | 102 | 1 | 16–25 Gy in 1–5 fractions | NR | 1-year: 46.3 |
| ***Adrenal Metastasis*** | | | | | |
| *Holy et al. (56) single centre (n=13)* | 13 | 1(62-66) | Median dose 40 Gy in 5 fractions | 21-month:77 | Median OS: 23 months |
| *Casamassima et al. (57) single center (n=48* | ? | 1 (1-2) | 36 Gy in 3 fractions | 2-year: 90 | 2-year: 14·5 |
| *Rudra et al. (58) single centre (n=10)* | 13 | 1 (1-2) | ? | 1-year: 73% | 1-year: 90% |
| ***Multiple organ*** | | | | | |
| *Salama et al. (59) single centre (n = 61)* | 113 | 2 (1–5) | 24–48 Gy in 3 fractions | 2-year: 52.7 | 2-year: 57 |
| *Milano et al. (25) single centre (n = 121)* | 293 | 2 (1–5) | 50 Gy in 10 fractions preferred | 2-year: 67 | 4-year: 28 |
| *Kao et al. (60) single centre (n = 21)* | 36 | 1 (1–5) | 40–60 Gy in 10 fractions | 1-year: 85 | 1-year: 75 |
| *Inoue et al. (61) single centre (n=44)* | 60 | NR (1-5) | 48 Gy in 4 fractions (adrenal)<br>35-60 Gy in 4-8 fractions | 3-year: 80 | 3-year: 39 |

Table 2: Selected series of extracranial stereotactic radiosurgery or stereotactic body radiation therapy for metastases from NSCLC.

| ***Study*** | *Number of Metastasis Treated* | *Sites Treated* | *SBRT Dose* | *Treated Metastasis Control Rate (%)* | *Median Survival (months)* | *Overall Survival Rate (%)* |
|---|---|---|---|---|---|---|
| *Hasselle et al. (64) single centre (n = 25)* | 62 | Lung, brain, bone, liver, adrenal, lymph nodes, Spleen and muscle | 50 Gy (5 Gy per dose) or 24–48 Gy (8–16 Gy per dose) | 1.5-year: 71 | 23 | 1.5-year: 52.9 |
| *Cheruvu et al. (65) single centre (n = 52)* | 70 | Lung, brain, bone and liver | 50–60 Gy in 5–10 fractions | NR | 20 | 2-year: 43 |
| *Wang* et al. (66) *single centre (n=14)* | 14 | Lung, brain and bone | 45-60 Gy in 3–5 fractions | 1-year: 83.9 | 19 | 1-year: 69.6 |
| *Weickhardt* et al. *(62) single centre (n=25)* | 31 | Lung, brain, bone, liver, adrenal and lymph nodes | 15-54 Gy in 1-5 fractions for SBRT/SRS (n=23)<br><br>WBRT (n=6) and conventional RT (n=2) also used | NR | Median PFS: 10.3 months | NR |
| *Yu* et al. *(63) single centre (n=18)* | 18 (only 3 received RT) | Lung, brain, bone, liver, adrenal and lymph nodes | NR<br><br>SBRT (n=1)<br>Conventional RT (n=2) | | 41 months | 5-year: 40<br>Overall median survival of 41 months |

*Multiple Organ Metastases*

The largest series of mixed oligometastatic disease is that of Milano and colleagues (22). The investigators recruited 121 patients with ≤5 metastases and delivered a median dose of 50 Gy in 5 Gy fractions over 2 weeks. These doses are at the lower end of the dose range presently used for SBRT. Most patients had lung, liver, or lymph-node metastases. The only grade 3 toxic effect was a non-malignant pleural and pericardial effusion, and no higher-grade adverse effects occurred. The 2-year and 4-year treated metastasis control rates were 77% and 74%, respectively, and the 4-year overall survival was 59%. Salama and colleagues (59) performed a dose-escalation trial in 61 patients with 113 metastases. Initially, patients were given 24 Gy in three fractions, which was increased sequentially to 48 Gy in three fractions. For those who received 24 Gy in three fractions, control of the treated metastases was poor at 45.7%, whereas in the four patients given 48 Gy in three fractions, 100% control was achieved.

In general, the toxicity of SBRT is mild to moderate. The proportion of patients with grade 3 acute or late adverse effects is less than 10%, and in many studies no grade 3 toxicity was recorded (3, 11, 15, 16, 55).

The simultaneous delivery of SBRT to multiple targets in multiple organs can be much more complicated than treating a single metastasis in a single organ. The entrance and exit dose contributions from the 5–13 (or more) radiation beams required to tightly conform the radiation dose around each tumor site must be considered (37-39). Although this planning is not particularly difficult if the metastases have wide anatomical distances between them, treating metastases in close proximity to each other, particularly when organ motion must be accounted for, can be complex (71). Thus, in the clinical settings described above, there is a need to explore the use of alternative dose/fractionation schemes and SBRT modalities. Proton beam radiation has not only the potential for normal tissue sparing that cannot be achieved with conformal photon techniques but also allows for treating multiple target sites and escalation of dose to levels that cannot be safely achieved with photons (37, 39). To date, there are no published studies on the use of proton beam SBRT in the management of oligometastatic disease.

Overall, these data suggest that SBRT can be an effective metastasis-directed therapy for patients with metastatic cancer. Similar to surgery, SBRT, when delivered to all known metastases, can result in long-term disease control (11). Further studies are needed to comprehensively integrate this therapy. Moreover, determining an optimal patient population for metastasis-directed SBRT is important as these treatments are resource-intensive, labor-intensive, and are associated with treatment-related toxicity.

## 2.2 Study Disease

Stage IV NSCLC

Lung cancer is the most frequent cause of cancer death amongst both men and women in the United States. An estimated 226,160 new cases were diagnosed, and 160,340 Americans were expected to die from lung cancer in 2012, accounting for approximately 28% of all cancer deaths (72, 73). About 87% of lung cancers are non-small cell in histology. About 35-40% of patients with NSCLC present with metastatic, stage IV disease. These patients are treated with cytotoxic, immunomodulatory, or targeted biological therapeutics, with the goals of limiting the progression of cancer and improving overall survival (74-76).

Although radiotherapy has been an integral treatment for patients with metastatic cancer over the past century, it is usually reserved for palliation of pain, dyspnea, bleeding, or neurological deficits among other indications. Definitive local therapies are effective in the eradication of early-stage primary NSCLC (6, 7, 9, 45). In the metastatic setting, however, local therapies such as surgery and SBRT can only be justified if patient outcomes are improved (68).

Mehta et al. used serial CT to monitor the number of individual metastatic sites and the number of organs involved in patients with advanced NSCLC who had been treated with chemotherapy (77). Of these patients, 50% had disease limited to the primary tumor and three or fewer metastatic lesions. In addition, 50% patients had stable or progressive disease in initially involved sites with no development of new metastatic lesions. Importantly, following first line chemotherapy, up to 64% of patients who develop disease progression did so in either the primary tumor or original sites of metastases. These observations support the clinical state of 'oligometastasis', elucidated by Hellman and Weichselbaum, who hypothesized that local control of oligometastasis could improve systemic control, progression free survival (PFS), and consequently prolong overall survival (OS) in a subset of patients (78, 79). Theoretically, if radical intervention (i.e., SBRT) could be delivered during an oligometastatic phase, the intervention could directly delay local disease progression in these patients (14, 80).

Few studies have evaluated the benefits of SBRT in the treatment of oligometastatic disease in stage IV NSCLC only. The most prominent study was reported by Hasselle et al. (64) who evaluated 22 stage IV NSCLC patients who received SBRT for the control of 62 individual lesions (median size 2.7cm) within the brain, lung, bone, liver, adrenal, lymph nodes, spleen, and muscle. The median dose and fraction dose to extracranial lesions were 50 and 5 Gy. Median OS and PFS were 22.7 and 7.6 months, respectively. The 18-month local control, distant control, OS, and PFS rates were 66.1%, 31.7%, 52.9%, and 28.0%, respectively. Results of this study and others demonstrate that SBRT to oligometastatic NSCLC provides durable local control of treated lesions and may provide long-term PFS in some patients (51, 59, 61, 65). What remains to be identified is the ideal population of stage IV NSCLC patients who are most likely to achieve prolonged disease free survival with SBRT.

Oncogene-driven NSCLC

Mutations and/or chromosomal rearrangements resulting in oncogene activation are responsible for the oncogenicity of a subset of NSCLC. These include activating mutations of the epidermal growth factor receptor (EGFR) tyrosine kinase, in addition to chromosomal rearrangements resulting in the activation of the anaplastic lymphoma kinase (ALK), and the c-ros oncogene 1 (ROS1) receptor tyrosine kinase.

EGFR mutations are the second most common oncogene mutations found in NSCLC, occurring in ~10% of all tumors. Patients with EGFR-mutant NSCLC respond well to EGFR tyrosine kinase inhibitors (TKI) such as erlotinib or afatinib. This has established EGFR mutations as a biomarker for TKI responsiveness (27, 32, 33, 81). Clinically, the use of EGFR TKI in EGFR-mutant patients is associated with an often dramatic response rate in ~70% of cases, compared to 20-30% response seen with the use of conventional chemotherapy. Importantly, EGFR TKI therapy prolongs the median PFS of EGFR mutant patients to 9-13 months for first/second generation inhibitors such as erlotinib and afatinib and about 18 months for third-generation osimertinib, which is significantly better than the 3-5 months median PFS of patients treated with chemotherapy regimens. Osimertinib is FDA approved as of April 2018 for use in first-line therapy. In addition,

the use of EGFR TKI is associated with better quality of life and less toxicity than conventional chemotherapy. EGFR TKI are used as first line treatment in the management of stage IV EGFR-mutant NSCLC (29, 31, 32, 82)(32a).

ALK chromosomal rearrangements are found in approximately 5% of NSCLC and define a distinct molecular subtype of lung cancer (33, 83, 84). Crizotinib is an oral small-molecule tyrosine kinase inhibitor which targets ALK, and ROS1 tyrosine kinases (85-88). Recently, a phase 3 trial comparing conventional chemotherapy to crizotinib in ALK positive advanced NSCLC reported response rates of 65% with crizotinib, compared to 20% with chemotherapy. Importantly, the median PFS was 7.7 months in patients treated with crizotinib and only 3.0 months in the chemotherapy group (89). Additional TKIs have become available in the past few years with subsequent prolongation of PFS, including alectinib which in first line therapy has a median PFS of at least 18-20 months (32b,c). These results and others have established the role of several TKIs in the systemic management of ALK positive advanced NSCLC patients.

ROS1 rearrangements occur in 1-2% of NSCLC and they represent another unique molecular subset of lung cancers (83, 90, 91). Crizotinib has also been shown to be effective in inhibiting the ROS1 tyrosine kinase thus providing anti-tumoral activity in ROS1 positive cancers. The preliminary results of a phase I trial of crizotinib (NCT00585195) in patients with advanced NSCLC harboring ROS1 gene rearrangement, were presented at ASCO and ESMO 2012 and demonstrated promising results with an objective response rate of 57% and a disease control rate of 80% after 2 months (Shaw et al, unpublished).

An important challenge to the success of TKI therapy is the development of drug resistance. Disease progression while on TKI therapy is thought to result from the growth of resistant clones that most commonly arise within sites of persistent disease (primary and metastatic) (34-36, 92-95). Of significance, failure to eradicate persistent disease has been associated with an increased risk of developing distance metastasis in various types of cancer (96). This highlights the importance of optimizing local disease control in order to lower the rate of distant failures and achieve prolonged PFS (96-98). SBRT is effective in controlling localized metastatic disease (80) and can potentially eliminate residual TKI-resistant clones, thereby reducing original site failure and potentially reducing the frequency of distant spread resulting from persistent original disease (Figure 2A). Therefore, the adjuvant use of SBRT for local control of residual disease in original sites following TKI therapy may extend PFS and OS of oncogene-driven stage IV NSCLC patients.

Of interest, there is room for potential synergy between SBRT and TKI in the management of metastatic oncogene-drive NSCLC. Effective targeted therapy against oncogene-driven NSCLC can eradicate micrometastatic disease and reduce metastatic lesions to a limited number that becomes amenable to aggressive local therapy with SBRT. Furthermore, according to the Norton–Simon hypothesis, the effectiveness of systemic agents is proportional to the growth rate of the tumor and the fastest tumor growth rates occur when tumors are not bulky (99, 100). Therefore, if aggressive local therapy (SBRT) can

downsize the primary tumor, the remaining tumor cells may become more sensitive to maintenance TKI therapy. As such, oncogene-driven NSCLC represents a potentially ideal patient population for consolidative SBRT aimed at decreasing the overall risk of distant failure by eradication of persistent and potentially drug resistant original disease, thereby improving PFS.

As SBRT has shown to benefit certain patients with metastatic disease, the development of treatment algorithms integrating SBRT with optimal systemic therapies based on histology-specific or molecular data are needed. Only three retrospective studies have reported results on stage IV oncogene-driven (EGFR-mutant) NSCLC patients treated with metastasis-directed SBRT and TKI (Table 2). Weickhardt et al. (62) retrospectively investigated the benefits of SBRT/SRS, whole brain radiation therapy, and palliative radiation therapy in 10 EGFR-mutant NSCLC patients deemed suitable for local therapy to central nervous system and/or limited systemic metastasis with continued treatment with erlotinib. Patients were only treated with SBRT upon disease progression and this was associated with more than 6 months of additional disease control. Yu et al. (63) treated 18 oligometastatic EGFR-mutant NSCLC patients who had developed acquired resistance to EGFR TKI with elective local therapy. Only 1 patient was treated with SBRT (to the lung) in this series. However, local therapy in these patients was associated with median time to progression of 10 months and a median survival time of 41 months. Wang et al. (66) treated 14 NSCLC patients (not limited to EGFR-mutant disease) with disease progression after platinum-based chemotherapy with gefitinib and SBRT directed at progressive metastatic disease. Treatment was well tolerated. The 1-year local control and OS rates were 83.9% and 69.6%, respectively, and the median PFS and OS times were 7 and 19 months, respectively.

Together, these limited data suggest that oncogene-driven NSCLC is amenable to SBRT for the treatment of oligometastatic disease when used in conjunction with continued TKI therapy. Combining radiation with TKI such as erlotinib has been shown to be safe and well tolerated by patients. In addition, this approach has been associated with seemingly prolonged PFS at least in EGFR-mutant NSCLC, and there is no data to suggest that ALK or ROS1-translocated cancers would behave differently

The patterns of disease failure following TKI treatment in oncogene-driven NSCLC patients is poorly described in the literature. In review of a cohort of 47 patients with EGFR-mutant NSCLC treated with EGFR TKI at the Massachusetts General Hospital, we defined progression in sites of original disease (primary and metastatic sites) as "original sites failure" (OF) and the development of new metastases outside areas that originally contained disease as "distant failures" (DF) (Sequist et al., unpublished) (Figure 2). The cumulative frequency of OF only as the first site of recurrence was 39%, DF only was 13%, and concurrent DF and OF was 28%, observed at 18 months after initiation of TKI therapy, which is 6 months after a median PFS of about 12 months for first/second-generation EGFR TKIs. This pattern of failure is consistent with other reports on the general population of NSCLC progressing after chemotherapy.

## 2.3 Rationale

SBRT is established as a therapy for medically inoperable early-stage NSCLC, and its role has been recently explored in stage IV NSCLC with low metastatic burden or oligometastatic disease. Studies have shown that SBRT can achieve high rates of treated-metastasis control for patients with limited pulmonary, hepatic, adrenal, and spinal metastases (11, 15, 16, 18, 53, 58). Stereotactic radiosurgery (SRS) is used for the treatment of intracranial metastases (101).

SBRT is generally well tolerated and associated with a low risk of severe toxicity. The use of metastasis-directed SBRT was shown to improve disease-free survival in selected NSCLC patients with low burden metastatic disease (64). However, the ideal population of stage IV NSCLC patients who are most likely to achieve prolonged disease free survival with SBRT remain to be identified.

Targeted therapy against oncogene-driven NSCLC may eradicate micrometastatic disease and reduce metastatic lesions to a limited number that becomes amenable to aggressive local therapy. Furthermore, SBRT can downsize the primary tumor and metastatic sites making the remaining tumor cells more sensitive to targeted therapies. In addition, SBRT to residual disease following TKI therapy may eradicate drug resistant clones that give rise to TKI resistant disease and eventual treatment failure in original and new, distant sites of disease. As such, oncogene-driven NSCLC represents a potentially ideal patient population for consolidative SBRT aimed at decreasing the probability of distant spread by reducing locally persistent and potentially drug resistant disease that can spread hematogenously.

In summary, we hypothesize that persistent tumor in sites of original disease can give rise to distant metastases and that localized SBRT to residual, active sites of original disease may reduce the incidence of DF occurring concurrently or in close temporal sequence with OF (96-98). The local control rate of metastases treated by SBRT is generally reported to be 80% (11, 15, 16, 26, 70, 80). Therefore, based on our own and literature data and assuming that EGFR-mutant NSCLC will behave similarly as other oncogene-driven NSCLC, we hypothesize that we can reduce the frequency of patients with concomitant OF and DF by 20%. This will lower the frequency of all DF (with or without concomitant OF) from 40% to 20% (Figure 2). The frequency of patients with DF with or without OF as site of first failure will be assessed at 12 months after initiation of SBRT, which will be approximately 18 months after initiation of TKI (to be comparable with our historical data, see Section 2.2).

Reported studies of combined therapy with EGFR TKI and SBRT in stage IV NSCLC patients showed improved disease control and disease-free survival with the addition of SBRT (62, 63, 66). These studies however only used SBRT to treat metastases at time of progression. To our knowledge, the proposed study will be the first to prospectively assess the impact of consolidative SBRT (to sites of residual, non-progressive primary and/or oligometastatic disease) in stage IV EGFR-mutant and other oncogene-driven NSCLC patients undergoing TKI therapy. It will also be the first study to utilize proton beam SBRT in the treatment of metastatic lung cancer. Furthermore, the study may improve the outcome of a subgroup of metastatic oncogene-driven NSCLC patients and may identify oligometastatic oncogene-driven NSCLC as an ideal population for consolidative SBRT.

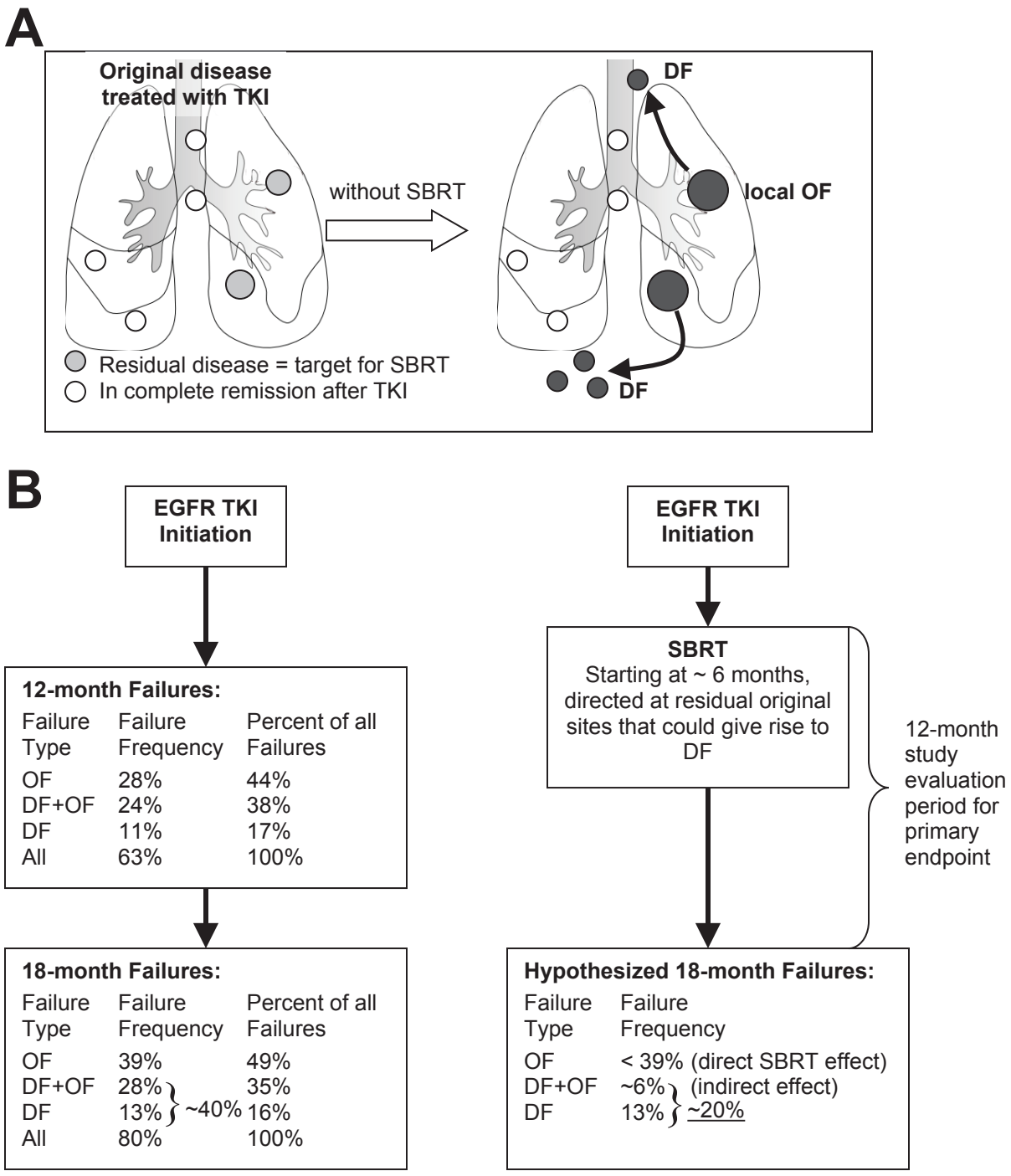


Figure 2. Overall hypothesis and preliminary data. (A) Illustration of hypothesized indirect effect of local therapy (SBRT) on DF. SBRT may directly reduce OF frequency by eliminating residual sites of disease. SBRT may indirectly reduce DF by eliminating residual sites of disease containing TKI resistant tumor that can give rise to subsequent DF. (B) Patterns of failure from a MGH cohort of patients with advanced EGFR-mutant NSCLC treated with first-generation TKIs (n=47) and hypothesized effect of SBRT. OF, failure in original sites; DF, failure in (new) distant sites.

### 2.4 Correlative Studies Background

N/A

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

**3.1.1** Participants must have histologically or cytologically confirmed non-small cell lung cancer (NSCLC) with any actionable mutation or translocation in EGFR, ALK, or ROS1

**3.1.2** Documented history of clinical stage IV (Any T, any N, M1a/b) disease as per AJCC Staging system 7th edition (Appendix A).

**3.1.3** Participants must be within 6 months of initiating treatment with a traditional TKI such as erlotinib, gefinitib, afatanib or crizotinib, which specifically targets the actionable mutation their tumor harbors. Participants receiving TKIs typically associated with a long PFS, such as first-line osimertinib or alectinib, should be within 12 months of TKI treatment. Other TKIs are acceptable with approval of Study PI..

**3.1.4** Participants must have stable or responding systemic disease to TKI (no evidence of progression) on the most recent staging studies. The required staging studies are: (1) A re-staging CT scan of the chest +/- abdomen with IV contrast (unless medically contraindicated) within 2 months of study enrollment; and (2) in patients with known brain metastasis, or to investigate patients with new onset of neurologic symptoms that may suggest metastasis to the brain, Brain MRI with gadolinium, or head CT scan with IV contrast will be required within 2 months of study enrollment. The complete extent of the current residual systemic disease must be deemed amenable to SBRT as per review of imaging studies by a radiation oncologist involved in this trial. This will be based on the following criteria:

Lung: 1-3 lesions (including the primary) of maximum size 5 cm in longest diameter. A minimum size 1 cm in the longest diameter is recommended. (Patients with a malignant pleural effusion prior to the start of TKI therapy will be considered eligible for SBRT if there is complete radiographic resolution of the effusion while on systemic therapy);
Spine: Bone lesions must be limited to the spine. A maximum of 2 spinal metastases will be considered for SBRT, with each site spanning 1-3 vertebral bodies. A minimum size of 1 cm in longest diameter is recommended. SBRT may target sclerotic lesions that persist following TKI therapy;
GI: 1-4 liver metastases of maximum size 5 cm in longest diameter and/or 1-2 adrenal metastases of maximum 4 cm size in longest diameter. A minimum

size of 1 cm in longest diameter is recommended.
In addition:
CNS: 1-4 brain metastases of maximum size 3cm in longest diameter. However, these should be treated with standard-of-care SRS and will not be defined as target lesions for purposes of this protocol. There is no minimum size requirement for treatment of brain lesions but small foci of potential disease (1-4 mm size) detected on high-resolution MRI may not be clinically relevant and do not count towards the maximum number of 4 brain metastases as per the treating radiation oncologist's discretion and in line with institutional practice.

A maximum number of 5 target lesions outside the brain, excluding the lung primary, is recommended to ensure that enrollment is limited to patients with low-burden disease and that treatments can be delivered within the specified time frame. This is not an absolute requirement as situations may exist when more than 5 metastatic targets are appropriate in the treating radiation oncologist's clinical judgment, for example when nearby lesions can be included in a single treatment field.

**3.1.5** History of prior radiation therapy to brain or skeleton is allowed, but should have occurred > 2 months from enrollment.

**3.1.6** Age at least 18 years.

**3.1.7** Life expectancy of greater than 6 months.

**3.1.8** ECOG performance status ≤2 (see Appendix B).

**3.1.9** Radiation is a known teratogenic agent. Thus, 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 and for the duration of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

**3.1.10** Ability to understand and the willingness to sign a written informed consent document.

### 3.2 Exclusion Criteria

*Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.*

**3.2.1** Subjects deemed to have residual hilar or mediastinal lymph node disease (defined as nodal size > 1cm in short-axis diameter on CT scan), since SBRT to mediastinal or hilar structures is potentially associated with high toxicity. Non-malignant etiologies for enlarged lymph nodes may be evaluated per standard clinical practice.

**3.2.2** Participants who have received prior radiation therapy to anatomical sites other than brain or skeleton.

**3.2.3** Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

**3.2.4** Patients who are pacemaker or defibrillator-dependent as these devices may not be operated concurrently with delivery of proton beam radiation.

**3.2.5** Pregnant or lactating women, as treatment involves unforeseeable risks to the embryo or fetus. Female subjects of childbearing potential must indicate to their physician that there is not a possibility of being pregnant at the time of enrollment or have a negative pregnancy test prior to the initiation of radiation therapy.

### 3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Both men and women of all races and ethnic groups are eligible for this trial. Lung cancer affects men and women, and people of all race and socioeconomic class. We do not expect the inclusion and exclusion criteria to negatively affect enrollment of underrepresented populations.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

### 4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #**:** REGIST-101) must be followed.

### 4.3 General Guidelines for Other Participating Institutions

N/A

### 4.4 Registration Process for Other Participating Institutions

N/A

# 5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

This is a phase II prospective trial of 30 patients to establish the efficacy and safety of integrating consolidative SBRT into the management of Stage IV oncogene-driven NSCLC with low-burden metastatic disease. Proton beam radiation will be administered in the Francis H. Burr Proton Therapy Center (FHBPTC) at MGH. Linear-accelerator-based SBRT with photons, if needed, will be administered in the MGH Clark Center for Radiation Oncology. SBRT will be delivered as once-daily treatments over 1-10 fractions.

## 5.1 Pre-treatment Assessment

This trial will accrue patients with pathologically confirmed oncogene-driven metastatic NSCLC that meet the eligibility criteria listed in Section 3.1. All accrued patients will be evaluated by a radiation oncologist within 1 month of study registration. This preliminary evaluation will include history and physical examination, including weight and assessment of ECOG performance status. A re-staging CT scan of the chest with/without abdomen with IV contrast (unless medically contraindicated) will be obtained as per standard of care within 2 months of study enrollment to determine the extent of disease (including spinal metastasis) and aid in radiation planning. Brain MRI with gadolinium, or head CT scan with IV contrast will be required within 2 months of study registration in patients with known brain metastasis, or to investigate patients with new onset of neurologic symptoms that may suggest metastasis to the brain. Spine MRI with gadolinium may be obtained at baseline for radiation planning purposes if a subject has spine metastasis as well as in follow-up as per standard clinical practice. Imaging will be obtained as per standard of care within 2 months of study enrollment.

SBRT-eligible sites are limited to lungs, liver, adrenals, and spine (limits outlined in Table 3). A total number of 5 targets outside the brain and excluding the lung primary is recommended. Patients with newly diagnosed brain metastases (1-4 lesions), may be treated with standard-of-care SRS. There is no minimum size requirement for treatment of brain lesions but small foci of potential disease (1-4 mm size) detected on high-resolution MRI may not be clinically relevant and do not count towards the maximum number of 4 brain metastases as per the treating radiation oncologist's discretion and in line with institutional practice.

## 5.2 SBRT Planning and Treatment

### 5.2.1 Simulation and Treatment Planning

5.2.1.1 Simulation: All simulations will be performed according to standard institutional practice for the different anatomical sites of this protocol (Lung, Liver, Adrenals, Spine). This may include placement of fiducials markers prior to simulation to guide precise radiation delivery to tumor

targets that move with respiration, such as tumors in the liver and the lungs. Fiducials placement will typically be done via a CT-guided transcutaneous approach as per institutional practice and as per standard-of-care for stereotactic and stereotactic-like treatments (109-111).

5.2.1.2 Delineation of tumor target volumes and organs at risk (OAR): Gross tumor and OAR for each anatomical site will be contoured according to standard institutional practice. For each anatomical site, 2 or more of the target lesions can be irradiated concurrently at the discretion of the treating physician.

5.2.1.3 Treatment planning: Passively or actively scanned proton beam radiation should be used for all anatomical sites unless for a given subject the use of conformal photon techniques (3D conformal, intensity-modulated radiation therapy, or volumetric arc) is judged superior by the treating physician, or unless there would be undue delay of treatment due to resource availability. Treatment planning will be performed according to standard institutional practice for each anatomical site. SBRT planning will vary among patients with multiple metastases based on the size, geometry and location of these metastases. When metastases are widely separated in the body (for example, one in the upper lobe of the lung and another in the adrenal gland) little overlap can be expected and each may be planned independently of each other. However, in other cases, such as concurrent lung tumor and thoracic spine metastasis, careful consideration should be given to the avoidance of beam overlap.

5.2.1.4 Dose Prescription and Fractionation:

- The optimal dose and fractionation for each anatomical site will be dictated by the OARs in close proximity to the target site, and thus will vary between subjects according to institutional practice and standard-of-care (112)..
- Depending on size and location, it is recommended that the tumor target be covered by one of the dose fractionations listed in Table 3.

Table 3. Recommended criteria and dose fractionation for SBRT targeted sites

| **Site** | **Target** | **Dose and Fractionation** |
|---|---|---|
| **Lung** | Primary plus 1-2 metastatic targets<br><br>Maximum size: 5 cm largest diameter | 6-12 Gy x 4-10 fractions |
| **Liver** | 1-4 targets<br>Maximum size: 5 cm largest diameter | 6-10 Gy x 5-10 fractions |
| **Adrenals** | 1-2 targets<br>Maximum size: 4 cm largest diameter | 5-8 Gy x 5-10 fractions |
| **Spine** | 1-2 targets, each target can span 1-3 vertebral bodies. | 18 Gy single fraction |

A minimum size of 1 cm in largest diameter is recommended for all sites mainly due minimum field size constraints that could affect dosimetry. It may be clinically indicated to treat lesions < 1 cm for example if they are avid on FDG-PET. This is at the discretion of the treating radiation oncologist in accordance with departmental routine clinical care guidelines.

### 5.2.2 Treatment delivery

5.2.2.1 Location: All treatments will be delivered at the Francis H. Burr Proton Treatment Center or the Clark Center for Radiation Oncology at MGH.

5.2.2.2 Treatment Start: Following enrollment, radiation treatment should be initiated at the earliest possible time as per standard-of-care, which in most cases is expected to be within 4 weeks though a longer interval is acceptable. Because of the need to assess TKI response it is unlikely that treatments will start within 4-5 months of TKI treatment. For participants enrolling at the end of the 6-month TKI window for traditional drugs such as erlotinib, afatainib, or crizotinib, treatment will likely commence > 6 months after TKI start. Taken together, it is anticipated that radiation treatments will commence on average by 6 months (in most cases, between 5 and 7 months), so that primary endpoint assessment at 12 months after SBRT start will be comparable to historical outcomes at 18 months after TKI start (see 14.1 Primary Endpoint). For the same reason, participants who are on TKIs associated with longer PFS times, such as osimertinib, treatment should occur within about 12 months of TKI treatment.

5.2.2.3 Timing: Treatments may be given on subsequent days with approximately 24 hours inter-fraction interval. A more protracted course is allowed also. Treatments may commence on any day of the week. Treatments may be delivered with 1-3 isocenters per session at the treating physician's discretion. However, only one anatomical site should be treated at a given time. For treatment of any two anatomical sites, the minimum and maximum interval between the last treatment of the previously anatomical site and the first treatment of the next anatomical site should be 1 week and 2 months, respectively. The overall treatment duration, i.e., 1$^{st}$ day of SBRT delivery until final day of SBRT delivery for all anatomical sites to be treated should not exceed 4 months.

5.2.2.4 On rare occasion, proton beam radiation becomes unavailable due to technical problems. Photon-based SBRT may be used as a back-up only if the duration of proton unavailability would make the overall treatment time for a given site treatment extend beyond 14 elapsed days (counted from day of the first to the last fraction for a given anatomical site).

5.2.2.5 Quality Assurance: All SBRT treatment plans will be reviewed for QA per the standard Department of Radiation Oncology practices for all patients treated.

## 5.3 General Concomitant Medication and Supportive Care Guidelines

Eligible subjects will be on specific TKI treatments corresponding to their driver mutation. TKI will be held on days when patients are receiving SBRT.

### 5.4 Duration of Therapy

Treatments may be given on subsequent days with approximately 24 hour interfraction interval or spread out over 2 weeks. Missed treatments due to technical problems, patient factors, or other factors will be added at the end of the treatment course. It is recommended that the overall duration of each treatment course (per anatomical site) should not exceed 14 elapsed days. The total duration of SBRT courses, i.e., first day of any SBRT until final day of any SBRT, should not exceed 4 months.

Participants will be followed by the treating radiation oncologist prior to the start and upon completion of each SBRT course. Patients receiving a 4-10 fraction SBRT course will also be evaluated during weekly treatment visits. Assessments during and immediately following the completion of SBRT are intended to record and manage acute side effects that patients may experience.

Treatments may be discontinued for any of the following events:

- Development of additional sites of metastasis during the 4-month SBRT course.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

### 5.5 Duration of Follow Up

Participants will be followed for 2 years after the completion of treatment. Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Follow up assessments will include physical examinations, toxicity and adverse event assessment, and imaging tests, as described in Section 9. If needed, participants will be assessed and managed for any treatment related acute toxicity 6 weeks after completion of SBRT. Participants will be evaluated clinically and radiographically for tumor progression and assessed and managed, if necessary, for any SBRT-related late toxicity every 3 months. It is unlikely that many patients with metastatic NSCLC will be alive beyond 2-3 years. Participants distant to MGH will be encouraged to follow up at the treating center, or send medical records and imaging studies obtained locally at the specified follow-up times.

### 5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator,

Henning Willers, M.D.
617-726-5184
hwillers@partners.org

# 6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used.

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

## 6.1 Anticipated Toxicities

Radiation side effects are divided into those that occur acutely (during radiation and up to 3 months after radiation) and those that occur later (>3 months post-radiation). Acute side effects are typically common and transient, while late normal tissue complications are generally rare but they can be severe and/or permanent. Late complications are considered dose-limiting (102).

Late toxicity is relatively uncommon and reported rates of grade ≥3 complications following SBRT as per this protocol are generally <5%. Treatment related deaths are very rare, occurring in less than 1% of cases (11, 15, 16, 22, 59).

### 6.1.1 Expected Toxicities of SBRT

Abnormalities in blood work may or may be a direct or indirect effect of SBRT.

**Pulmonary**

Common (>10%)

- Fatigue
- Dermatitis

Uncommon (<10%)

- Nausea/decrease appetite
- Cough
- Esophagitis
- Moist skin desquamation
- Pneumonitis
- Dyspnea

- Hypoxia
- Hemoptysis
- Rib fracture/chest wall pain
- Pericarditis

Rare (<1%)

- Fistula
- Brachial plexopathy
- Transverse myelitis
- Congestive heart failure
- Heart attack
- Vascular aneurysm or rupture

**Gastrointestinal**

Common (>10%)

- Abdominal pain
- Fatigue
- Skin irritation
- Nausea and vomiting
-

Uncommon (<10%)

- Esophagitis
- Dysphagia
- Loose stools

Rare but serious (<1%)

- Kidney damage
- Bowel scarring, obstruction and/or perforation requiring surgery
- Veno-occlusive disease
- Radiation-induced liver disease/cirrhosis
- Transverse myelopathy

**Spine**

The side effects or risks of spine SBRT are variable and dependent on the vertebral level being treated. This includes:

Common (>20%)

- Pain flare
- Fatigue
- Skin irritation

Uncommon (<20%)

- Mucositis
- Esophagitis
- Nausea and vomiting
- Loose stools
- Transient neuropathy
- Dysphagia
- Vertebral fracture

Rare but serious (<1%)

- Transverse myelopathy
- Kidney damage
- Bowel scarring requiring surgery

### 6.2 Toxicity Management

No side effects specific to proton SBRT, as compared to photon SBRT which is in routine clinical use, are expected.

No serious acute side effects are expected during the short course of treatment. In the unlikely event of any grade 3 or 4 acute toxicity, there will be a treatment break until the toxicity resolves to grade 2 or less.

No specific therapy exists for radiation-induced fatigue. Mild to moderate dermatitis, typically occurring 3-4 weeks after radiation, may be managed with an alcohol-free emollient such as Aquaphor® or hydrocortisone ointment as needed. Pneumonitis should be managed per standard clinical practice, including a trial of antibiotic, prednisone 60 mg daily by mouth until symptom improvement followed by a slow taper, with or without oxygen support. All expected side effects as listed above will be managed according to standard institutional practice for each anatomical site.

### 6.3 Dose Modifications/Delays

Any grade 3 or 4 acute toxicity, related to radiation therapy, will result in a treatment break until it resolves to grade 2 or less. If a treatment break of > 14 days is needed, the patient will be removed from study.

## 7. DRUG FORMULATION AND ADMINISTRATION

N/A

## 8. CORRELATIVE/SPECIAL STUDIES

8.1 Participants are allowed to enroll on separate IRB-approved protocols as long as those do not involve investigational or commercial agents or therapies intended to treat the participant's residual cancer.

8.2 Research Biopsy

As part of the current protocol, participants will be offered an *optional* tumor biopsy at the time of standard-of-care fiducials placement for guiding stereotactic radiation treatments (109-111). There exists strong scientific rationale for studying the response of oncogene-addicted tumors to TKI before drug resistance and clinical progression occur.

Currently, it is standard-of-care to re-biopsy a progressive primary tumor or metastasis to determine the mechanism of acquired TKI resistance and guide selection of next-line treatment (113). The identification of T790M resistance mechanism in EGFR-mutated NSCLC which can be targeted by third-generation TKI, is an example of this approach. However, treatment of TKI resistance remains challenging: Resistance mechanisms may be unknown or cannot be currently targeted, more than one resistance mechanism may occur in an individual, or resistance to third-generation TKI will develop (114-116). The vast majority of current research efforts are being directed at targeting tumors with acquired resistance to TKI. In contrast, opportunities to prevent the emergence of resistance remain vastly understudied. Tumor cells that survive inhibition of the oncogenic kinase may persist in a drug-tolerant state for some time and ultimately give rise to clones with acquired TKI resistance (117). This "persister" state has remained underappreciated as a potential therapeutic opportunity even though the stress responses to shutting down the driving oncogene likely create multiple survival dependencies.

The purpose of obtaining a research biopsy before clinical progression therefore is to identify novel therapeutic targets, which may benefit future patients. A potential benefit to the participant undergoing a biopsy is that evolving resistance mechanisms, such as T790M, may be identified prior to progression, which could inform treatment selection at the time of recurrence after protocol SBRT (i.e, obviating the need for a separate re-biopsy at time of clinical progression).

Tumor tissues for the analysis of TKI persisters will be obtained at the time of fiducials placement for SBRT, which will typically be a transcutaneous CT-guided approach. As fiducial placement will occur in or nearby the tumor, there will be the opportunity to obtain a needle biopsy from adjacent tumor. This will be done through the established needle access site and will not require an additional transcutaneous pass. No increase in bleeding risk is anticipated as fiducials will be placed away from pulmonary vessels. The length of the procedure will be minimally prolonged (by ~10 minutes), which poses no more than a minimal additional risk to the subject. In our own and published experience, combined fiducials placement and needle biopsy do not have a complication rate higher than either procedure alone (118, 119).

Expected toxicities for needle biopsy/fiducials placement are:

Common (>10%)

-Mild lung collapse (pneumothorax) not requiring treatment
-Localized minor bleeding within the biopsied organ not requiring treatment
-Self-limited mild blood coughing (hemoptysis)
-Localized mild pain at biopsy site

Uncommon (<10%)

-Lung collapse (pneumothorax) which may be painful and causing shortness of breath requiring hospital admission or/and placement of a drainage tube (chest tube)

Rare but serious (~1% or less)

-Major organ bleeding requiring transfusion or other intervention
-Entry of air into vessels and causing serious harm to organs such as brain or heart (air embolism)

Tumor biopsies will be fixed, frozen or cultured, and analyzed in the Engelman and Willers Laboratories at the MGH using an array of cellular, molecular, and other assays. These studies may include the generation of cell lines and xenografts. For complete analysis, samples may need to be sent to outside institutions such as the Broad Institute for genomic analysis and the National Institute of Standards and Technology for detection of oxidative DNA damage. Appropriate steps will be followed to protect health information. Collectively, these studies have the ultimate goal of identifying novel therapeutic targets to delay or prevent acquired TKI resistance.

## 9. STUDY CALENDAR

Baseline evaluation tests and scans are to be conducted within 2 months prior to registration as specified for each assessment. Exceptions are noted in the Table below. All assessments must be performed prior to administration of protocol treatment. All study assessments should be done within ±4 weeks of the protocol-specified date, unless otherwise noted.

| | Pre-Study | During each SBRT course (4-10 fractions) | Follow up |
|---|---|---|---|
| EGFR/ALK/ROS1 genotype | X | | |
| Documentation of stage IV NSCLC | X | | |
| TKI therapy [A] | X | | X |
| Evaluation by radiation oncologist | X[B] | X[C] | X[D] |
| Physical exam (including weight, and performance status) | X | | X[D] |
| Medical history | X | | X[D] |
| CBC, chemistry | X[F] | | X[G] |
| Toxicity and adverse events evaluation | X | X | X[D] |
| CT chest +/- abdomen | X[H] | | X[E] |
| Brain MRI or Head CT [I] | X | | X |
| Spine MRI [J] | X | | X |
| Informed study consent | X | | |
| Tumor Measure | X | | X[K] |

A. All patients must be receiving a TKI specifically targeting the actionable mutation harbored by their advanced NSCLC. The original date of TKI start should be recorded. SBRT must be initiated within approximately 6-12 months of TKI start, depending on the specific TKI treatment. TKI will be held on days of SBRT, resumed in the interval and resumed on the day after the final SBRT delivery.

B. The initial radiation oncology assessment should indicate that all radiation oncologists that will be involved in SBRT treatment for a given subject have reviewed the imaging studies and determined that all active disease in each anatomical site is amenable to SBRT. This assessment should be done within 1 month of registration.

C. Subjects will be seen by his/her radiation oncologist at least once and every 5 fractions during each SBRT course, and may be seen by his/her medical oncologist as per standard clinical care.

D. Following completion of all stereotactic treatments, subjects should continue follow-up as per standard of care, which typically includes surveillance scans every 3 months. This should entail visits with either medical oncology or radiation oncology or both. For assessment and management, if necessary, of any

acute toxicity, subjects may be seen if needed at 6 weeks (+/- 4 weeks) after the final day of SBRT. Imaging does not need to be performed at this follow-up unless clinically indicated. For subsequent study evaluations, subjects should be seen every 3 months (+/- 4 weeks). Each follow-up visit should be associated with toxicity and adverse events monitoring and history & physical.

E. CT scan of the chest +/- abdomen will be obtained every 3 months +/- 4 weeks, per standard of care. CT scans outside this schedule will be allowed if needed per standard of care, and will not be marked as a minor deviation.

F. At baseline, CBC with differential, basic metabolic panel (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), liver function tests (albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST).

G. During follow-up visits, CBC and chemicals will be drawn at the discretion of the treating physician.

H. CT scan of the chest with or without abdomen with intravenous contrast depending on disease extent as per standard practice (unless medically contraindicated or subject refuses). Additional scans such as CT neck or pelvis may be added based on disease extent and per standard-of-care. An additional PET scan may be obtained if clinically indicated as per standard clinical practice. Imaging will be obtained as per standard of care within 2 months of study enrollment.

I. Brain MRI with gadolinium or CT of the head with intravenous contrast should be obtained at baseline and in follow up of patients known to have brain metastasis or to investigate patients with neurologic symptoms that may suggest the development of new brain metastasis. Imaging will be obtained as per standard of care within 2 months of study enrollment and at the discretion of the treating physician.

J. Spine MRI with gadolinium may be obtained at baseline for radiation planning purposes if a subject has spine metastasis as well as in follow-up as per standard clinical practice. Imaging will be obtained as per standard of care within 2 months of study enrollment and at the discretion of the treating physician.

K. Tumor measurements are not required for every scan in follow up. Tumor measurements will be conducted when changes are visible to assess for tumor response and progression. For study data purposes, any scan reporting progression, as well as the scan immediately prior to that scan, will be assessed as described in Section 10 below.

# 10. MEASUREMENT OF EFFECT

## 10.1 Antitumor Effect– Solid Tumors

Tumor response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (103). Changes in the diameter (one-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Additional definitions beyond the RECIST guidelines are incorporated to define local lung primary and metastasis control (LC) following SBRT. Local response and control of lung tumors are often difficult to define due to radiographic radiation pneumonitis and fibrosis. Furthermore, the development of mass-like consolidation after lung SBRT has been reported (104, 105), further complicating the assessment of local control. In addition, RECIST assessments will not apply to the development of brain metastases and are limited for spine metastases.

### **10.1.1** Definitions

Evaluable for toxicity: All participants who receive at least one fraction of SBRT will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response: Only those participants who have measurable residual disease in response to TKI therapy, have completed their prescribed SBRT course, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression in targeted sites of residual disease or die prior to completion of SBRT will also be considered evaluable. However, patients that develop new sites of metastasis prior to the end of their SBRT course will be disqualified from the study).

As detailed below, for the purpose of this protocol, we will use the following definitions:

1. Original sites = extent of disease at presentation before TKI was started
   1a. Original sites that persist after start of TKI and that will be treated by SBRT = target lesions
   1b. Original sites in which there has been a complete response during TKI treatment = non-target lesions
   Failure in these sites will be classified as OF.

2. Distant sites = new sites of distant metastases distinct from original sites developing after SBRT = non-target lesions.
   Failure in these sites will be classified as DF.

### **10.1.2** Disease Parameters

Measurable disease:

Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter >=10 mm using conventional techniques (CT, MRI). Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Patients enrolled to this protocol will have stage IV NSCLC (Ant T, any N, and M1) NSCLC. At time of treatment, they should have stable residual primary/metastatic disease in no more than 4 extra-cranial anatomical sites within the lung (primary and metastatic), liver, adrenals, and spine.

Non-measurable disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

Non-measurable disease may occur as disease progression (nodal or distant) after completion of SBRT, but should not be present prior to therapy.

Target lesion:

The primary lung tumor in addition to the metastatic tumor sites treated with SBRT should be identified as the **t**arget lesions, and recorded and measured at baseline and with each follow-up imaging evaluation. Target lesions for the specified organs will be limited to 3 lesions in the lung (primary and 2 metastatic targets), 4 in the liver, 2 in the adrenal and 2 in the spine (Table 3). The longest diameter (LD) for the target lesions will be calculated from the pre-study CT scan obtained at time of study enrollment, following initial response to TKI and prior to initiating SBRT. This will be reported as the baseline LD. If there is appreciable interval growth of the target lesion seen at the time of CT planning for SBRT, this will be used as the new baseline LD. The baseline LD will be used as a reference by which to characterize the objective tumor response.

For follow-up assessment, diagnostic CT scans performed using a <5 mm contiguous reconstruction algorithm taken as part of scheduled protocol follow-up are preferred as the method of evaluation for response of lung, liver and adrenal lesions. MRI scans will be performed for the follow up evaluation of response in treated spinal metastasis as per institutional practice.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, in lung tumors bronchial or bronchiolar damage typically cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, additional assessments, such as PET/CT scanning and/or biopsy should be considered as per standard clinical practice.

Non-target lesions:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

More specifically, the definition of non-target lesions also applies to sites of original disease (diagnosed at presentation, before TKI therapy initiation), which following response to TKI become non-measurable disease and therefore are not targeted with SBRT. Such lesions should be identified as non-target lesions and should also be recorded at baseline and at each follow-up. Disease progression in this specific type of non-target lesions will be taken into consideration for the evaluation of local failure and original site failure (defined below).

### **10.1.3** Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment.

Conventional CT: Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm, with axials cuts of no more than 5 mm, and 2.5 mm cuts are recommended as per institutional practice at MGH. Intravenous contrast should be used unless there is a medical contraindication or the patient refuses.

FDG PET and PET/CT: The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (106). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular

attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. However, PET scans will only be ordered as part of standard clinical care.

Cytology, Histology: Biopsy confirmation may be sought, as clinically indicated, to document local recurrence or disease progression elsewhere.

MRI: Spine MRI with gadolinium may be used for diagnosis and to aid in the SBRT planning for treatment of active spinal metastasis, unless medically contra-indicated or the participant refuses. MRI with gadolinium may be used for the assessment of liver metastasis not well visualized on CT scans.

Special consideration will be used for the evaluation of bone lesions, based on the following:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

**10.1.4** Response Criteria

10.1.4.1 Evaluation of Target Lesions

Primary and metastatic lung target lesions

Complete Response (CR): Disappearance of the target lesion on CT image evaluation.

Partial Response (PR): At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started.

Local Enlargement (LE): At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; based on CT image evaluation. Local response and control of lung tumors are often difficult to define due to radiographic radiation pneumonitis and fibrosis. Therefore, if the criteria for LE are met, the patient may undergo a PET scan imaging or a direct biopsy of the targeted

tumor if clinically indicated. This information may be used for a determination as to whether original site failure (OF) exists as defined below.

Local Control (LC): The absence of LE in a target lesion treated with SBRT.

Metastatic liver/adrenal target lesions

Complete Response (CR): Disappearance of the target lesion on CT image evaluation.

Partial Response (PR): At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT image evaluation.

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

Progressive Disease (PD): At least a 20% increase in the sum of the largest diameters of target lesions, taking as reference the smallest sum on study this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Local Control (LC): The absence of PD in SBRT treated target lesions.

Metastatic spine target lesions

Spine MRI of the spinal region treated will be done as per standard clinical care but 3-month intervals in the first 2 years are recommended. Disease will be evaluated as:

Complete Response (CR): Disappearance of the target lesion on MRI image evaluation.

Responsive Disease: At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD. Evaluation will be made based on MRI scans.

Stable Disease: Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for PD below, taking as reference the baseline LD.

Progressive Disease/Local Failure: At least a 10% increase in the sum of the largest diameters of target lesion seen on each of 2 consecutive MRI scans, taking as reference the baseline LD.

Marginal Failure: the appearance of new lesions within one vertebral body space above or below the PTV

Local Control: the absence of progressive disease and/or marginal failure.

10.1.4.2 Evaluation of Non-Target Lesions

Definition of New Lesion: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions.

Progressive Disease (PD): Appearance of one or more new lesions (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions and /or overall level of substantial worsening that merits change of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

10.1.4.3 Evaluation of Best Overall Response

N/A

**10.1.5** Duration of Response

N/A

**10.1.6** Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of TKI therapy to time of objective progressive disease.

**10.1.7** Patterns of First Failure:

Progression will be divided into two categories: Original sites failure (OF) and distant failure (DF) (with and without concomitant OF). Death will also be regarded as a progression event.

Original Sites Failure (OF):

Refers to both target and non-target lesions (Table 4).

Target lesions: OF is defined as evidence of progressive disease (PD) (as defined above) within the primary and/or individual metastatic target lesions treated with SBRT. For primary lung lesions, PET-positive or biopsy-confirmed marginal failures within 2 cm of the gross target volume (GTV), will be counted as OF. The EORTC criteria for post-treatment PET evaluation may be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathologic for cancer recurrence vs. inflammation (107).

Non-Target lesions: OF is defined as evidence of progressive disease (PD) in metastatic sites that were diagnosed at presentation, prior to TKI therapy, but deemed non-target lesions (defined above), and therefore were not treated with SBRT.

Distant failure (DF): This is defined as the radiographic appearance of a new metastatic lesion having a dimension of at least 1 cm, in a site that was not identified at disease presentation prior to initiating TKI therapy (Table 4). For primary lung lesions, intra-thoracic failure at least 2 cm away from the GTV will also be scored as DF. Failure with intracranial metastasis should be confirmed by MRI with gadolinium.

**10.1.8** Response Review

All response assessments will be made by the study PI or a protocol co-investigator. Biopsy of suspected local failures or progressive disease will only be done if indicated per standard clinical practice, for example to determine mechanisms of resistance to TKI.

### 10.2 Antitumor Effect – Hematologic Tumors

N/A

### 10.3 Other Response Parameters

N/A

Table 4: Evaluation of overall response and patterns of failure

| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Pattern of First Failure** |
|---|---|---|---|---|
| CR | CR | None | CR | None |
| CR | Non-CR/Non-PD | None | PR | None |
| CR | Not evaluated | None | PR | None |
| PR | Non-CR/Non-PD/Not evaluated | None | PR | None |
| SD | Non-CR/Non-PD/Not evaluated | None | SD | None |
| PD | Any | None | PD | OF |
| Any | PD* | None | PD | OF |
| Any | Any | Yes | PD | DF (+/- OF) |

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

# 11. ADVERSE EVENT REPORTING REQUIREMENTS

## 11.1 Definitions

### 11.1.1 Adverse Event (AE)

An adverse event (AE) 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.

An AE of Special Interest includes hepatic injury defined by the following alterations of liver parameters (measured in the same blood draw sample): for patients with normal AST/ALT and bilirubin at baseline, an elevation of AST and/or ALT above > 3 fold ULN combined with an elevation of bilirubin above > 2 fold ULN. Patients showing these lab abnormalities need to be followed up appropriately.

### 11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical

intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

**11.1.3** Severity of adverse events

The severity of the AE should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

**11.1.4** Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.4.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of study treatment (SBRT). For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study treatment.

11.1.4.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list or when it is not included in the informed consent document as a potential risk.

**11.1.5** 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.

## 11.2 Procedures for AE and SAE Recording and Reporting

Reporting participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

## 11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

## 11.4 Reporting to the Study Sponsor

### 11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Henning Willers, MD, PI
Tel. 617-726-5184
Fax. 617-726-3603
hwillers@partners.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

**11.4.2** Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

## 11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

### 11.6 Reporting to the Food and Drug Administration (FDA)

N/A

### 11.7 Reporting to the NIH Office of Biotechnology Activities (OBA)

N/A

### 11.8 Reporting to the Institutional Biosafety Committee (IBC)

N/A

### 11.9 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

### 11.10 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB 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. DATA AND SAFETY MONITORING

## 12.1 Data Reporting

### 12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and monitor data for this study.

### 12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

| **Form** | **Submission Timeline** |
|---|---|
| Eligibility Checklist | Complete prior to registration with OnCore |
| On Study Form | Within 14 days of registration |
| Treatment Form | Within 10 days of completion of treatment |
| Toxicity and Adverse Event Report Form | Within 10 days of completion of treatment and within 10 days of protocol specified follow up visit |
| Measurement/Response Form | Within 14 days of registration and within 10 days of protocol specified follow up visit |
| | |
| Off Treatment/Off Study Form | Within 14 days of completing treatment or being taken off study for any reason |
| Follow up/Survival Form | Within 14 days of the protocol defined follow up visit date or call |

## 12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet as required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

# 13. REGULATORY CONSIDERATIONS

## 13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

## 13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

## 13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

### 13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

### 13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

### 13.6 Multi-center Guidelines

N/A

### 13.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

N/A

## 14. STATISTICAL CONSIDERATIONS

Recent studies have explored the benefits of metastasis-directed SBRT in low metastatic burden or oligometastatic stage IV NSCLC. These studies have revealed that SBRT can achieve high rates of treated-metastasis control for patients with limited pulmonary, hepatic, adrenal, and spinal metastases. Local control of individual metastases in this setting may potentially result in longer PFS and better outcomes in patients with low burden metastatic NSCLC.

Despite the overall theoretical benefits of SBRT in stage IV lung cancer, there has not been a prospective clinical trial of consolidative SBRT in oncogene-driven stage IV NSCLC. To assess the efficacy of integrating SBRT with targeted therapy and to establish a role for SBRT in the management of metastatic NSCLC, we will conduct phase II study of SBRT in 30 patients with low burden metastatic oncogene-driven NSCLC.

We hypothesize that persistent tumor in sites of original disease can give rise to distant metastases and that localized SBRT to persistent sites of original disease may reduce the incidence of DF occurring concurrently or in close temporal sequence with OF. The local control rate of metastases treated by SBRT is generally reported to be ~80%. We, therefore, hypothesize that we can reduce the frequency of combined OF and DF by ~20%, thereby lowering the frequency of all DF (with or without OF) as first site of failure from ~40% to 20% (see also Figure 2).

### 14.1 Study Design/Endpoints

The main objective of this study is to evaluate the impact of SBRT on the frequency of patients with DF (with or without concurrent OF) in oncogene-driven NSCLC patients with residual oligometastatic disease at 12 months after initiation of SBRT, which on average will correspond to 18-24 months since TKI induction therapy.

Secondary Endpoints

1) To describe toxicities of treatment using CTCAE v4.0.
2) To determine median PFS time
3) To analyze the pattern of original and distant site failures (OF and DF)
4) To determine 2-year local control rate of treated lesions
5) To determine median overall survival time and 2-year overall survival rate

### 14.2 Sample Size/Accrual Rate

The target sample size will be 30 patients. We anticipate a very low drop out rate (<5%) since the target population will mainly consist of healthy patients who are relatively young and non-smokers, and death of non-cancer causes or loss to follow-up would be very unlikely. If we were to observe DF with or without concomitant OF in 8 or fewer of the 30 patients at their 12-month evaluation, 87% power is achieved to detect a 20% reduction in the rate of DF with concomitant OF, which would therefore drop from an

overall frequency of 40% DF (based on results from a review of EGFR-mutant NSCLC patients treated with TKI at MGH) to the hypothesized 20%. The decision rule is associated with 9% probability of accepting the efficacy of adjuvant SBRT if the underlying rate of DF were unchanged from 40%. As noted above, we do not anticipate that any subjects will have died of non-cancer-related causes (i.e., without any failure) before the primary study endpoint, 12 months after SBRT, is reached. We acknowledge that any deaths of other causes will reduce the statistical power. Lastly, any subjects developing failure prior to completion of SBRT (see section 5.5) will be removed from the study and replaced, i.e., will not count towards the target sample size of 30 patients.

At MGH, about 50-60 patients with EGFR/ALK/ROS positive NSCLC are started on selective TKI per year, per a recent re-review of clinical practice data. Data from us and other recent reports have indicated that 10-20% of such patients may be eligible for consolidation SBRT, and in our review of patients in our practice we currently estimate that about 9 patients per year are eligible for SBRT. Assuming a ~80% accrual rate from all eligible patients we now expect to accrue 7 participants per year (adjusted from a previous estimate of 10 subjects per year). We estimate that it will take an additional 2 years to complete enrollment of 30 subjects and then complete follow-up to report results on the primary endpoint of frequency of DF at 1 yr post-SBRT.

Following the completion of planned SBRT treatments, patients will continue to receive standard of care therapy which would ordinarily involve continuation of maintenance TKI therapy until there is confirmed disease progression. Since the median PFS of TKI-treated oncogene-driven NSCLC patients is approximately 12 months for traditional TKIs and approximately 18 months or longer for newer drugs such as osimertinib used in first line, an evaluation time point set at 12 months following commencement of SBRT treatments, i.e., on average 18-24 months from TKI initiation will be sufficient to report the majority of failures.

Patients will be followed for 2 years after treatment or until death, whichever occurs first. Follow up examination and imaging studies will be scheduled as per standard clinical care for patients receiving TKI or other systemic therapy but intervals of 3 months for two years is recommended. Upon each follow-up visit, patients will be assessed for disease control and treatment toxicity.

| **Accrual Targets** | | | | | |
|---|---|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | | | |
| | **Females** | | **Males** | | **Total** |
| Hispanic or Latino | 1 | + | 0 | = | 1 |
| Not Hispanic or Latino | 14 | + | 15 | = | 29 |
| **Ethnic Category: Total of all subjects** | 15 | + | 15 | = | 30 |
| **Racial Category** | | | | | |
| American Indian or Alaskan Native | 0 | + | 0 | = | 0 |
| Asian | 0 | + | 0 | = | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Black or African American | 1 | + | 1 | = | 2 |
| Native Hawaiian or other Pacific Islander | 0 | + | 0 | = | 0 |
| White | 14 | + | 14 | = | 28 |
| **Racial Category: Total of all subjects** | 15 | + | 15 | = | 30 |

## 14.3 Stratification Factors

N/A

## 14.4 Analysis of Secondary Endpoints

### 14.4.1 Adverse events

Subjects will be tabulated by adverse events and grade. The frequency of any adverse events, as well as Grade 2-5 adverse events will be reported by CTCAE v4.0 criteria. Frequencies of acute toxicities as well as crude and actuarial rates of late normal tissue reactions (> 90 days after completion of radiation) will be calculated.

### 14.4.2 Progression-free survival

Radiographic tumor response and progression will be described based on RECIST criteria as detailed in Section 10.1. Progression-Free Survival (PFS) is defined as the duration of time from documented start of TKI therapy to time of objective progressive disease. Death will also be regarded as a progression event. For the calculation of PFS times, the Kaplan-Meier estimate will be reported with 95% confidence intervals using Greenwood's formula.

### 14.4.3 Assessment of pattern of failures

Progression will be divided into two categories: Original sites failure (OF) and distant failure (DF) (with and without concomitant OF). Crude frequencies and actuarial rates of original sites failure (OF) (primary or metastatic sites) as the first site of failure, as defined in Section 10.1, as well as crude frequencies and actuarial rates of distant failures (DF) as the first site of failure (with or without concomitant OF) will be calculated. OF is defined as disease progression in sites (primary and/or metastatic) that were present at diagnosis of metastatic NSCLC, prior to TKI initiation (includes both target and non-target lesions). DF are defined as development of new sites of metastases outside areas that originally contained disease. The diagnosis of OF with concomitant DF requires the detection of new sites of disease on the same follow up scan diagnosing progression in sites of

original disease (primary and metastatic sites). Original site and distant failures will be considered as individual events in the calculation of PFS.

#### 14.4.4 Local control of irradiated lesions

Local control (LC) is defined by the absence of progressive disease in target lesions treated with SBRT. The duration of LC is defined as the time period between the completion of SBRT to the time of objective progressive disease.

#### 14.4.5 Overall survival

Overall survival (OS) is defined as the duration of time from the start of documented TKI therapy to time of death. For the calculation of OS times, the Kaplan-Meier estimate will be reported with 95% confidence intervals using Greenwood's formula

### 14.5 Reporting and Exclusions

#### 14.5.1 Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first dose of radiation.

#### 14.5.2 Evaluation of response

Patients who received SBRT will be evaluated for response to treatment. Each participant should be assigned one of the following categories (based on the definitions of treatment outcome defined in Section 10.1):

1) Alive without evidence of OF or DF,
2) Alive with OF as first failure only,
3) Alive with DF (with or without concurrent OF) as first failure only,
5) Early death from malignancy,
6) Early death from toxicity,
7) Early death from other cause,
8) Unknown (not assessable, insufficient data).

By arbitrary convention, category 8 usually designates the "unknown" status of any type of data in a clinical database.

For each participant, the best clinical tumor response should be categorized as:

For lung primary and metastatic target lesions
a) complete response, or
b) partial response, or
c) stable disease, or
d) local enlargement

For metastatic target lesions within the liver, adrenals and spine
a) complete response, or
b) partial response, or
c) stable disease, or
d) local failure

## 15. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. A report is planned to be published in a peer-reviewed journal and that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three years after the end of data collection. Authorship will be based on rules established in previously published guidelines (108).

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APPENDICES

## Appendix A – AJCC 7th edition lung cancer staging

### 17. Definition of TNM:

**Primary tumor (T)**

- TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus). The uncommon superficial spreading tumor of any size is classified as T1 even when extending to the main bronchus, as long as the invasive component is limited to the bronchial wall.
    - T1a: Tumor ≤2 cm in greatest dimension
    - T1b: Tumor >2 cm but ≤3 cm in greatest dimension
- T2: Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm)
        - Involves the main bronchus, ≥2 cm or more distal to the carina
        - Invades the visceral pleura
        - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
    - T2a: Tumor >3 cm but ≤5 cm in greatest dimension
    - T2b: Tumor >5 cm but ≤7 cm in greatest dimension
- T3: >7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
- A tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

- T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

**Regional lymph nodes (N)**

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
- N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

**Distant metastasis (M)**

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1a: Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion
- M1b: Distant metastasis

### 17.1 Stage Grouping

| | | | |
|---|---|---|---|
| Occult Carcinoma | TX | N0 | M0 |
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1a,b | N0 | M0 |
| Stage IB | T2a | N0 | M0 |
| Stage IIA | T1a,b | N1 | M0 |
| | T2a | N1 | M0 |
| | T2b | N0 | M0 |
| Stage IIB | T2b | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1, T2 | N2 | M0 |
| | T3 | N1, N2 | M0 |
| | T4 | N0, N1 | M0 |
| Stage IIIB | T4 | N2 | M0 |
| | Any T | Any N | M0 |
| Stage IV | Any T | Any N | M1a,b |

**Appendix B: Performance Status Criteria**

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Description | 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. |