(RTOG 0813) SEAMLESS PHASE I/II STUDY OF STEREOTACTIC LUNG RADIOTHERAPY (SBRT) FOR EARLY STAGE, CENTRALLY LOCATED NON-SMALL CELL LUNG CANCER (NSCLC) IN MEDICALLY INOPERABLE PATIENTS

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Primary Objective

Phase I Portion

To determine the maximal tolerated dose (MTD) of SBRT for centrally-located NSCLC and the efficacy of that dose in patients who are not operative candidates

Phase II Portion

To estimate the local control rate at the MTD of SBRT

Secondary Objectives

- To estimate rates of ≥ grade 3 CTCAE, v. 3.0 adverse events other than a dose-limiting toxicity (DLT) which is possibly, probably, or definitely related to treatment and which occurs within 1 year from the start of SBRT;
- To estimate rates of late (> 1 year from start of SBRT) adverse events;
- To estimate the local control and progression-free and overall survival rates for patients treated with this regimen;

Tertiary Objectives (Exploratory)

- To study if molecular markers (proteomic or genomic) in the blood circulation prior to, during the course of treatment (between the third and fourth dose of SBRT), and at the first follow-up after SBRT predict 2-year local control, the occurrence of treatment-related grade ≥ 2 pulmonary adverse events, or the occurrence of treatment-related grade ≥ 2 non-pulmonary

adverse events; data will be analyzed in conjunction with other lung SBRT studies, including operable and inoperable patients.
- To analyze the prognostic significance of comorbidity status; data will be analyzed in conjunction with other SBRT studies, including operable and inoperable patients;
- To document tumor motion and inter-fraction (setup) errors.

Schema:

The starting RT dose for the study will be 10 Gy x 5 fractions every 2 days, over 1½ - 2 weeks (total dose of 50 Gy). The subsequent dose levels will escalate dose by 0.5 Gy per fraction (i.e., a 2.5 Gy total dose) to a maximum dose of 12 Gy x 5 fractions (TD 60 Gy in 5 fractions). Several lower dose levels will be employed if unacceptable dose-limiting toxicity (DLT) is seen with the planned starting dose of 10 Gy. All treatment plans will have to respect the organ-at-risk doses.

Criteria for Inclusion of Subjects:

- Pathologically (histologically or cytologically) proven diagnosis of non-small cell lung cancer (NSCLC);
- Stage T1-2, N0, M0 (AJCC Staging, 6th Ed.), tumor size ≤ 5 cm, prior to registration, based upon the following minimum diagnostic workup
- History/physical examination within 4 weeks prior to registration;
- Evaluation by an experienced thoracic cancer surgeon within 12 weeks prior to registration; the primary tumor must be deemed technically resectable by an experienced thoracic cancer

clinician, with a reasonable possibility of obtaining a gross total resection with negative margins, defined as a potentially curative resection (PCR). However, the patient must have underlying physiological medical problems that would prohibit a PCR due to a low probability of tolerating general anesthesia, the operation, the post-operative recovery period, or the removal of adjacent functioning lung. These types of patients with severe underlying health problems are deemed "medically inoperable." Standard justification for deeming a patient medically inoperable based on pulmonary function for surgical resection of NSCLC will include any of the following: Baseline FEV1 < 40% predicted, post-operative FEV1 < 30% predicted; severely reduced diffusion capacity; baseline hypoxemia and/or hypercapnia; exercise oxygen consumption < 50% predicted; severe pulmonary hypertension; diabetes mellitus with severe end organ damage; severe cerebral, cardiac, or peripheral vascular disease; or severe chronic heart disease.

- Imaging as follows:

1. CT scan with contrast (unless medically contraindicated) within 8 weeks of registration. The CT scan will include the entirety of both lungs, the mediastinum, liver and adrenal glands; the primary tumor dimensions will be measured on CT. **Note**: Patients with lesions that cannot be visualized by CT scan are not eligible for the study.
2. Whole body positron emission tomography (PET) scan within 8 weeks of registration, using FDG with adequate visualization of the primary tumor and draining lymph node basins in the hilar and mediastinal regions.
3. Patients with hilar or mediastinal lymph nodes ≤ 1 cm and no abnormal hilar or mediastinal uptake on PET will be considered N0. Mediastinal lymph node sampling by any technique is allowed but not required. Patients with > 1 cm hilar or mediastinal lymph nodes on CT or abnormal PET (including suspicious but nondiagnostic uptake) may still be eligible if directed tissue biopsies of all abnormally identified areas are negative for cancer.

- Zubrod Performance Status 0-2 within 4 weeks prior to registration;
- Age ≥ 18;
- Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right

and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi). [See figure below] Tumors that are immediately adjacent to mediastinal or pericardial pleura also are considered central tumors and are eligible for this protocol.

- Patients must have measurable disease.
- Routine spirometry, lung volumes, diffusion capacity, and arterial blood gases within 12 weeks prior to registration;
- Pleural effusion, if present, must be deemed too small to tap under CT guidance and must not be evident on chest x-ray. Pleural effusion that appears on chest x-ray will be permitted only after thoracotomy or other invasive procedure(s).
- Negative serum or urine pregnancy test within 1 week prior to registration for women of childbearing potential;
- Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment)
- Patients must provide study-specific informed consent prior to any protocol specified procedures.

Criteria for Exclusion of Subjects:

- Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 2 years (e.g., carcinomas *in situ* of the breast, oral cavity, or cervix are permissible); previous lung cancer, if the patient is disease-free for a minimum of 2 years is permitted.
- Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- Prior chemotherapy for the study cancer;
- Plans for the patient to receive other local therapy (including standard fractionated radiotherapy and/or surgery) while on this study, except at disease progression;
- Plans for the patient to receive systemic therapy (including standard chemotherapy or biologic targeted agents), while on this study, except at disease progression.