

FAST FACTS

NRG LU002 - MAINTENANCE SYSTEMIC THERAPY VERSUS CONSOLIDATIVE STEREOTACTIC BODY RADIATION THERAPY (SBRT) PLUS MAINTENANCE SYSTEMIC THERAPY FOR LIMITED METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC): A RANDOMIZED PHASE II/III TRIAL

NRG-LU002

SCHEMA (22-June-2018)

<p>Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy</p> <p>Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery</p>	<p>S T R A T I F I C A T E D</p>	<p>Histology:</p> <p>Squamous vs. Non-squamous</p> <p>Systemic Therapy: Immunotherapy* vs Cytotoxic Chemotherapy</p>	<p>Arm 1: Maintenance systemic therapy alone**</p> <p>Arm 2: SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.**</p> <p>** As noted in Section 5</p>
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Inclusion Criteria

1. Pathologically proven diagnosis of NSCLC, with metastases (stage IV disease) present prior to registration. This includes patients newly diagnosed with metastatic disease or those initially diagnosed and treated for stage I-III NSCLC who ultimately develop metastases;
2. Appropriate stage for study entry based on the following diagnostic workup:
 - History/physical examination within 30 days prior to registration;
 - Imaging proof of limited metastatic disease and response to therapy/stable disease, by at least CT chest through the adrenals or PET/CT, within 30 days prior to registration;
3. Age ≥ 18 ;
4. Zubrod Performance Status 0, 1, or 2 within 30 days prior to registration
5. Adequate organ and hematologic/bone marrow function within 30 days prior to registration and at least 14 days after last dose of first-line/induction systemic therapy, defined as follows:
 - Aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN) or $\leq 5 \times$ ULN with metastatic liver disease
 - Total bilirubin $\leq 1.5 \times$ ULN
 - Absolute neutrophil count (ANC) ≥ 500 cells/mm³

- Creatinine clearance ≥ 45 mL/min/1.73 m² for patients with creatinine levels above institutional normal
 - Platelets $\geq 50,000$ cells/mm³
6. Negative serum pregnancy test within one week prior to registration for females of childbearing potential;
 7. Patients must have received first-line/induction systemic therapy (at least 4 cycles) and achieved stable disease or a partial response;
 8. Prior systemic therapy as part of concurrent treatment approach for previously diagnosed stage III NSCLC, as adjuvant therapy for previously resected NSCLC, or for other previous cancers is permitted;
 9. Prior radiotherapy for patients with brain metastases prior to enrollment is acceptable.
 10. Patients must have measurable disease at baseline and 3 or fewer discrete, extracranial metastatic disease sites that are technically amenable to SBRT. Some examples of what constitutes specific radiation treatment sites defining distinct metastatic disease sites are as follows:
 - a) A lesion in each adrenal gland represents 2 of 3 sites of metastatic disease allowed to be treated on protocol;
 - b) Similarly to NRG study RTOG 0631, disease in 2 contiguous vertebral bodies (with up to 6 cm of paraspinal extension) can represent one site of disease in the spine; non-contiguous lesions in vertebral bodies separated by one vertebral body free of disease should be viewed as 2 sites of treatment; and
 - c) Two lesions in such close proximity to one another that treatment with one isocenter is more accurate and safer in the liver, lungs, or other similar anatomic locations should be viewed as one site of metastatic disease treatment. Anatomic sites that may be treated with SBRT are listed in section 5.2;
 11. For de novo stage IV NSCLC patients (patients with metastatic disease at first presentation), primary disease must be treatable with local therapy in the form of SBRT or hypofractionated radiation. If the primary disease is found in the peripheral or central lung parenchyma without nodal disease, for instance, SBRT may be employed. If primary disease is more advanced with involvement of the mediastinum (T4 tumor, N1-N3 disease, etc.), these volumes should be technically treatable with hypofractionated radiation;
 12. If primary disease in the thoracic cavity was previously treated with local therapy in the form of surgery or radiation, any new local/regional disease recurrence should be technically treatable with SBRT or hypofractionated radiation after induction systemic therapy;
 13. Patients must be registered within 35 days of administration of the last dose of first-line/induction systemic therapy;
 14. The patient or a legally authorized representative must provide study-specific informed consent prior to study entry;
 15. Prior radiotherapy for patients with brain metastases prior to enrollment is acceptable.
 16. Patients with brain metastases are eligible if these lesions have been previously treated and the patients have no clinical or radiographic evidence of progression prior to enrollment.
 17. At least one site of metastatic disease or primary disease must be determined by radiation oncologist to be treatable with radiation.
 18. Subjects may receive palliative radiotherapy for symptomatic metastases or primary disease prior to enrollment provided that there is at least one other non-irradiated lesion amenable to LCT at the time of enrollment.

Exclusion Criteria

1. Clinical or radiologic evidence of new, untreated, and/or progressive brain metastases prior to registration after induction systemic therapy;
2. Cutaneous metastasis of NSCLC;
3. Metastatic disease invading the esophagus, stomach, intestines, or mesenteric lymph nodes;

4. Prior invasive malignancy (except non-melanomatous skin cancer, low or intermediate risk prostate cancer, or in situ carcinoma of breast, oral cavity, skin, or cervix) unless disease free for a minimum of one year.
5. Metastases located within 3 cm of previously irradiated (< 3Gy per fraction) structures if:
 - Spinal cord previously irradiated to > 40 Gy
 - Brachial plexus previously irradiated to > 50 Gy
 - Small intestine, large intestine, or stomach previously irradiated to > 45 Gy
 - Brainstem previously irradiated to > 50 Gy
 - Lung previously irradiated with prior V20Gy > 35%
6. Patients receiving targeted therapy (non-cytotoxic, non-immunotherapy based systemic therapy) for NSCLC in the first-line setting. Such designations would include but not be limited to treatments targeting EGFR mutant-positive or EML4-ALK mutant positive NSCLC in the first-line setting;
7. If a patient has progressed in previous areas of primary disease that received definitive doses of radiation, these patients would require re-irradiation in previous high dose anatomic areas and are not eligible for this study;
8. Patients with malignant pleural effusions that do not resolve after first-line systemic therapy. Patients with pleural effusions that have become too small for thoracentesis at the time of registration would be permitted on study, indicating a significant response to first-line systemic therapy;
9. Patients with more than 3 discrete locations of extra-cranial metastatic disease after first-line systemic therapy requiring more than 3 SBRT plans to cover these distinct metastatic disease entities;
10. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
11. Patients who are pregnant or nursing;
12. Participation in any investigational drug study (excluding non-oncology and/or symptom management studies) within 4 weeks prior to registration;
13. Known HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count \geq 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
14. Patients who received prior non-induction pembrolizumab, patients on chronic steroids or who have active autoimmune disease for which they received systemic treatment in the previous 2 years with corticosteroids, disease modifying agents, or immunosuppressive drugs. Replacement therapy (thyroxine, insulin or physiological corticosteroid replacement for adrenal or pituitary insufficiency) is allowed. Patients with active interstitial lung disease or who have a history of pneumonitis for which they had received glucocorticoids are not eligible.
15. Prior bevacizumab therapy is excluded.

Prior to registration checklist

1. Pathologic proof of NSCLC
2. Evaluation by a radiation oncologist
3. Performance status
4. Diagnostic CT chest
5. CMP
6. CBC/diff with ANC
7. Serum pregnancy
8. Whole blood, Serum , and plasma collection for banking