NRG-LU002

Report Based on Data Through: 04/30/2019

Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial

Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery	**S T R A T I F Y**	**Histology:** Squamous vs. Non-squamous **Systemic Therapy:** Immunotherapy* vs Cytotoxic Chemotherapy	**R A N D O M I Z E**	**Arm 1**: Maintenance systemic therapy alone** **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.** **** As noted in Section 5**

* Acceptable immunotherapy for NRG-LU002 is pembrolizumab.
** Randomization will be 2:1 between Arm 2 and 1.

Patients must be registered within 35 days of completion of induction systemic therapy if all eligibility requirements are met.

Systemic Therapy (see Section 5 for a list of treatment options):
(Arm 1): Maintenance systemic therapy should begin within 2 weeks of randomization.
(Arm 2): Radiation should begin within 2 weeks of randomization and maintenance systemic therapy should begin within 2 weeks of the completion of radiation. Maintenance systemic therapy must also begin within 3 weeks after completion of surgery if last local therapy modality.

Radiotherapy and Surgery for Local Therapy:
Investigators are *strongly* encouraged to directly contact the study PI and/or radiation oncology/surgery co-chairs about any questions concerning eligibility or concerns regarding radiation delivery (i.e., SBRT in the setting of concurrent SBRT/hypofractionated RT to the primary, SBRT in the setting of prior RT to the primary, SBRT to multiple sites, etc.) or surgical approaches (i.e., resection after thoracic radiation, extent of resections, resection techniques for metastatic sites, timing of resections and delivery of SBRT).

Study Chairs:	Puneeth Iyengar, MD, PhD	(Principal Investigator/Radiation Oncology)	[NRG Oncology]
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Activated: 04/07/2017

Status: Accruing

- **Study Description**
  NRG-LU002 is a randomized phase II/III trial designed to evaluate whether maintenance systemic therapy with or without local consolidative therapy will improve outcomes for patients with metastatic NSCLC with no evidence of progression and limited metastatic sites after first-line systemic therapy. The primary endpoint of the phase II portion of the study is progression-free survival, and for the phase III portion is overall survival. Patients must have no more than 3 sites of discrete, extracranial metastatic disease sites that are technically amenable to SBRT or resection (at least one disease site must be amenable to radiation). Patients with new, untreated, and/or progressive brain metastases are not eligible, nor are patients with metastatic disease invading the esophagus, stomach, intestines, or mesenteric lymph nodes if not a candidate for surgery for these lesions. Amendment 2 was broadcast on August 13, 2018, to allow for the use of immunotherapy as part of maintenance therapy and to allow the use of surgery as part of arm 2's local consolidative therapy (at least one lesion must be irradiated). Due to the anticipated better outcomes amongst patients receiving immunotherapy, the sample size was adjusted from 300 patients to 400 patients, and the anticipated monthly accrual was also changed from 6.6 patients per month to 9.5 patients per month. The study is also now stratified by the use of the type of systemic therapy to be used for maintenance: cytotoxic chemotherapy vs. immunotherapy.

- **Patient Accrual**
  Accrual was activated on April 7, 2017. Total accrual is 49 (Table 1). The monthly accrual rate over the last 6 months (5.7) is lower than projected (9.5). As of April 30, 2019, the median time of follow-up for vital status is 2.3 months. The first interim analysis is projected to occur in summer 2021.

- **Patient and Tumor Characteristics**
  No patients are ineligible for analysis (Table 2). The distribution by patient and tumor characteristics is shown in Table 3. Median (min-max) age is 66 years (51-85). Most patients are male (53.1%), white (87.8%), not Hispanic or Latino (91.8%), and had a Zubrod Performance Status of 1 (57.1%). As of April 30, 2019, 4 patients have withdrawn consent to follow-up, all 4 on Maintenance Therapy.

- **Adverse Events**
  Adverse events (AEs) were graded with CTCAE version 5. As of April 30, 2019 and regardless of attribution to treatment, there has been 1 patient (7.7%) with grade 4 AEs and 1 patient (7.7%) with grade 5 AEs reported on Maintenance Therapy, and 2 patients (11.1%) with grade 4 AEs and 2 patients (11.1%) with grade 5 AEs reported on LCT + Maintenance Therapy (Table 4). There are no notable differences in grade 4-5 rates by system organ class. All adverse events, regardless of attribution to protocol treatment, for which at least one grade 4 or grade 5 event has been reported are shown in Table 5. Since the last meeting report there was a new incidence of grade 5 AE reported in Maintenance Therapy arm (death NOS, unrelated to treatment), and three new incidences of grade 5 AE reported in LCT + Maintenance arm (one death NOS, unrelated to treatment; one respiratory failure, unrelated to treatment; one respiratory failure, probably related to treatment). There are no notable differences in grade 4-5 rates by term.

Table 1
NRG-LU002 Accrual Summary - Data as of 04/30/2019

Date activated to accrual:	April 7, 2017
Targeted sample size:	400
Projected monthly accrual*:	9.5
Average monthly accrual over last 6 months:	5.7
Projected accrual as of 04/30/2019:	92
Total accrual as of 04/30/2019:	49
Percent of projected accrual achieved as of 04/30/2019:	53.26%
Percent of total targeted accrual as of 04/30/2019:	16.33%
Projected completion date based on last 6 months accrual:	June 2024

*Little to no accrual was expected for the first 6 months of this study.

Table 2
NRG-LU002 Accrual/Eligibility - Data as of 04/30/2019

	Maintenance Therapy	LCT + Maintenance Therapy	Total
Randomized	23	26	49
Ineligible	0	0	0
Eligible	23	26	49

Table 3
Patient and Tumor Characteristics for All Eligible Patients in NRG-LU002 - Data as of 04/30/2019

	Maintenance Therapy		LCT + Maintenance Therapy		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)						
50 - 59	7	30.4	4	15.4	11	22.4
60 - 69	9	39.1	13	50.0	22	44.9
≥ 70	7	30.4	9	34.6	16	32.7
Gender						
Male	10	43.5	16	61.5	26	53.1
Female	13	56.5	10	38.5	23	46.9
Race						
Asian	1	4.3	1	3.8	2	4.1
Black or African American	4	17.4	0	0.0	4	8.2
White	18	78.3	25	96.2	43	87.8
Ethnicity						
Hispanic or Latino	0	0.0	1	3.8	1	2.0
Not Hispanic or Latino	23	100.0	22	84.6	45	91.8
Unknown	0	0.0	3	11.5	3	6.1
Zubrod Performance Status						
0	12	52.2	9	34.6	21	42.9
1	11	47.8	17	65.4	28	57.1
Histology*						
Non-Squamous cell carcinoma	18	78.3	20	76.9	38	77.6
Squamous cell carcinoma	5	21.7	6	23.1	11	22.4
Systemic Therapy Type*†	(n=17)		(n=21)		(n=38)	
Cytotoxic Chemotherapy	3	17.6	2	9.5	5	13.2

Table 3
Patient and Tumor Characteristics for All Eligible Patients in NRG-LU002 - Data as of 04/30/2019

Patient or Tumor Characteristic	Maintenance Therapy n	Maintenance Therapy %	LCT + Maintenance Therapy n	LCT + Maintenance Therapy %	Total n	Total %
Immunotherapy	14	82.4	19	90.5	33	86.8
Number of Lesions						
1	15	65.2	16	61.5	31	63.3
2	5	21.7	8	30.8	13	26.5
3	3	13.0	2	7.7	5	10.2
Consented to tissue/blood collection						
No	4	17.4	7	26.9	11	22.4
Yes	19	82.6	19	73.1	38	77.6
Total	23	100.0	26	100.0	49	100.0

*Stratification factor
†Only patients registered on or after August 13, 2018.

4 patients received no study treatment and are not included in adverse event tables.

Table 4
Distribution of NRG-LU002 Patients by Highest Grade Adverse Event by System Organ Class - Data as of 04/30/2019
For All Reported Adverse Events without Regard to Attribution

System Organ Class	Maintenance Therapy (n=13) n and (%) of Patients by Grade					LCT + Maintenance Therapy (n=18) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	1 (7.7)	5 (38.5)	4 (30.8)	1 (7.7)	1 (7.7)	3 (16.7)	5 (27.8)	4 (22.2)	2 (11.1)	2 (11.1)
Blood and lymphatic system disorders	1 (7.7)	0 (0.0)	2 (15.4)	0 (0.0)	0 (0.0)	3 (16.7)	0 (0.0)	4 (22.2)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (11.1)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	3 (23.1)	5 (38.5)	1 (7.7)	0 (0.0)	0 (0.0)	2 (11.1)	6 (33.3)	2 (11.1)	0 (0.0)	0 (0.0)

Table 4
Distribution of NRG-LU002 Patients by Highest Grade Adverse Event
by System Organ Class - Data as of 04/30/2019
For All Reported Adverse Events without Regard to Attribution

System Organ Class	Maintenance Therapy (n=13) n and (%) of Patients by Grade					LCT + Maintenance Therapy (n=18) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
General disorders and administration site conditions	5 (38.5)	3 (23.1)	0 (0.0)	0 (0.0)	1 (7.7)	6 (33.3)	3 (16.7)	2 (11.1)	0 (0.0)	1 (5.6)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	5 (38.5)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	3 (16.7)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (7.7)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	3 (23.1)	1 (7.7)	2 (15.4)	0 (0.0)	5 (27.8)	0 (0.0)	2 (11.1)	2 (11.1)	0 (0.0)
Metabolism and nutrition disorders	4 (30.8)	1 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	3 (16.7)	5 (27.8)	2 (11.1)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (23.1)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.6)	1 (5.6)	0 (0.0)	0 (0.0)
Nervous system disorders	2 (15.4)	3 (23.1)	1 (7.7)	0 (0.0)	0 (0.0)	2 (11.1)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	3 (23.1)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (7.7)	0 (0.0)	3 (23.1)	0 (0.0)	0 (0.0)	7 (38.9)	1 (5.6)	0 (0.0)	2 (11.1)	2 (11.1)
Skin and subcutaneous tissue disorders	3 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	1 (5.6)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 5.

Table 5
Distribution of NRG-LU002 Patients by Highest Grade Adverse Event
by Specific Adverse Event Term - Data as of 04/30/2019
For Selected Adverse Events without Regard to Attribution

System Organ Class/Term	Maintenance Therapy (n=13) n and (%) of Patients by Grade					LCT + Maintenance Therapy (n=18) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (38.5)	3 (23.1)	0 (0.0)	0 (0.0)	1 (7.7)	6 (33.3)	3 (16.7)	2 (11.1)	0 (0.0)	1 (5.6)
Death NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
INVESTIGATIONS	0 (0.0)	3 (23.1)	1 (7.7)	2 (15.4)	0 (0.0)	5 (27.8)	0 (0.0)	2 (11.1)	2 (11.1)	0 (0.0)
Creatinine increased	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	1 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.6)	1 (5.6)	0 (0.0)
Neutrophil count decreased	1 (7.7)	0 (0.0)	1 (7.7)	1 (7.7)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Platelet count decreased	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (7.7)	0 (0.0)	3 (23.1)	0 (0.0)	0 (0.0)	7 (38.9)	1 (5.6)	0 (0.0)	2 (11.1)	2 (11.1)
Hypoxia	0 (0.0)	1 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (11.1)	0 (0.0)
Pneumonitis	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.6)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (11.1)

Adverse events were graded with CTCAE version 5.
Only includes system organ classes and terms with at least one Grade 4 or Grade 5.
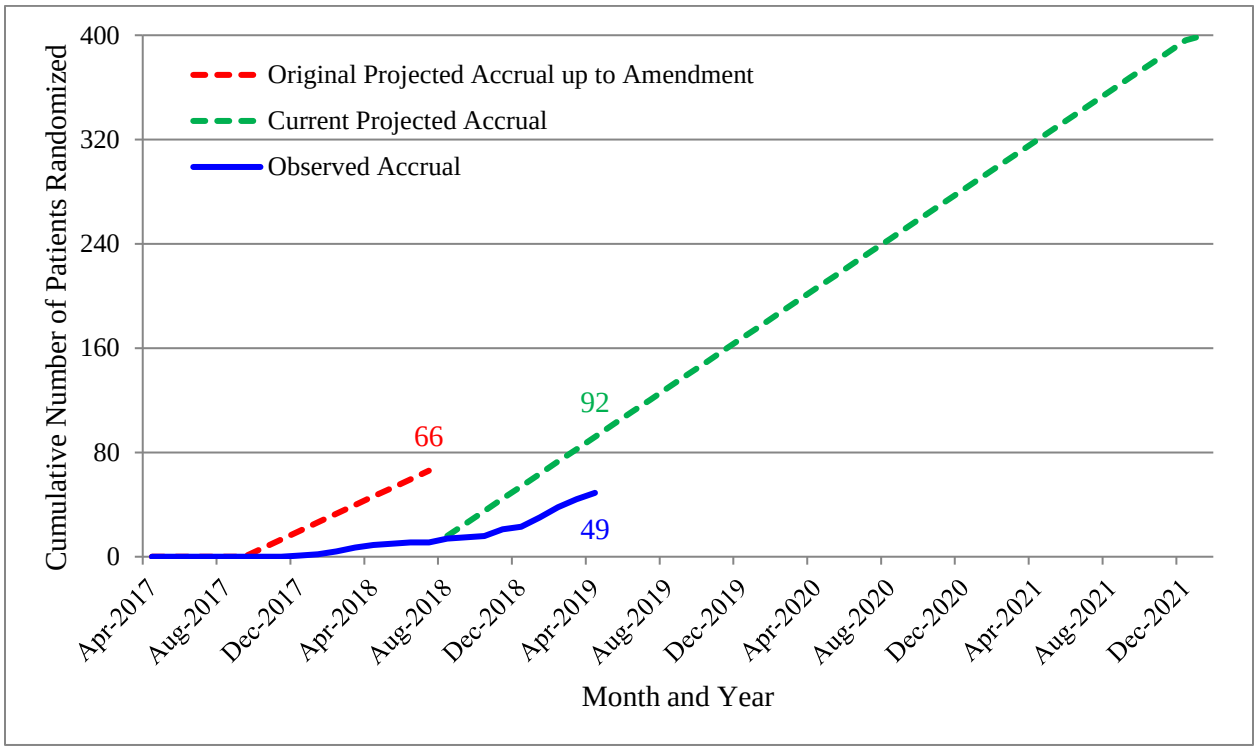
Figure 1
Cumulative Accrual for NRG-LU002 – Data as of 04/30/2019