NRG-LU001

Report Based on Data Through: 04/30/2019

Randomized Phase II Trial of Concurrent Chemoradiotherapy +/- Metformin HCL in Locally Advanced NSCLC

STRATIFY

Zubrod Performance Score
1. 0
2. 1

Histology
1. Squamous
2. Non-Squamous

Clinical Stage
1. IIIA
2. IIIB

RANDOMIZE

Arm 1:
Concurrent Chemoradiotherapy

RT: 60 Gy/30 fx with chemotherapy for 6 weeks

Followed by Consolidation Chemotherapy for 6 weeks

Arm 2:

MET Dose Escalation: 1000 mg to 2000 mg daily for 2 weeks

Concurrent Chemoradiotherapy + MET: RT: 60 Gy/30 fx with Chemotherapy and MET (2000 mg, p.o. daily) for 6 weeks

Consolidation Chemotherapy + MET: Consolidation chemotherapy for 6 weeks and MET (2000 mg p.o. daily) for 10 weeks.

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Activated: 08/25/2014

Closed: 12/15/2016

Status: Follow-up, pending primary outcome analysis

- **Study Description**
  This is a two-armed randomized phase II study designed to determine whether metformin added to chemoradiotherapy can improve progression-free survival in patients with locally advanced non-small cell lung cancer. The primary endpoint is progression-free survival.

- **Patient Accrual**
  Accrual was activated on August 25, 2014, and closed December 15, 2016. Total accrual is 170 (Table 1). As of April 30, 2019, the median time of follow-up for vital status is 25.9 months. Results will be presented at ASCO 2019.

- **Patient and Tumor Characteristics**
  Three patients on No Metformin are ineligible for analysis (Table 2). The distribution by patient and tumor characteristics is shown in Table 3. Median (min-max) age is 64 years (43-86). Most patients are male (58.1%), white (82.0%), not Hispanic or Latino (94.0%), and had a Zubrod Performance Status of 1 (50.3%). As of April 30, 2019, 18 patients have withdrawn consent to follow-up: 5 on No Metformin and 13 on Metformin.

- **Adverse Events**
  Adverse events (AEs) were graded with CTCAE version 4. As of April 30, 2019 and regardless of attribution to treatment, there have been 17 patients (21.5%) with grade 4 AEs and 4 patients (5.1%) with grade 5 AEs reported on No Metformin, and 21 patients (25.3%) with grade 4 AEs and 1 patient (1.2%) with a grade 5 AE reported on Metformin (Table 4). There are no notable differences in rates of grade 4 or 5 AEs 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. There are no notable differences in rates of grade 4 or 5 AEs by term. There were no new grade 5 AEs since the last report, and all reported grade 5 AEs were reported as either unrelated or unlikely related to treatment.

Table 1
NRG-LU001 Accrual Summary - Data as of 04/30/2019

Date activated to accrual:	August 25, 2014
Targeted sample size:	168
Projected monthly accrual*:	7
Average monthly accrual over last 6 months:	9.7
Total accrual:	170

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

Table 2
NRG-LU001 Accrual/Eligibility - Data as of 04/30/2019

	No Metformin	Metformin	Total
Randomized	84	86	170
Ineligible	3	0	3
Eligible	81	86	167

Table 3
Patient and Tumor Characteristics for All Eligible Patients in NRG-LU001 - Data as of 04/30/2019

	No Metformin		Metformin		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)						
≤ 49	6	7.4	3	3.5	9	5.4
50 - 59	22	27.2	26	30.2	48	28.7
60 - 69	29	35.8	35	40.7	64	38.3
≥ 70	24	29.6	22	25.6	46	27.5
Gender						
Male	48	59.3	49	57.0	97	58.1
Female	33	40.7	37	43.0	70	41.9
Race						
American Indian or Alaska Native	2	2.5	0	0.0	2	1.2
Asian	5	6.2	2	2.3	7	4.2
Black or African American	7	8.6	7	8.1	14	8.4
Native Hawaiian or Other Pacific Islander	0	0.0	1	1.2	1	0.6
White	67	82.7	70	81.4	137	82.0
More than one race	0	0.0	1	1.2	1	0.6
Unknown	0	0.0	5	5.8	5	3.0
Ethnicity						
Hispanic or Latino	3	3.7	1	1.2	4	2.4
Not Hispanic or Latino	77	95.1	80	93.0	157	94.0
Unknown	1	1.2	5	5.8	6	3.6
Zubrod Performance Status						
0	38	46.9	45	52.3	83	49.7
1	43	53.1	41	47.7	84	50.3
AJCC Stage						
IIIA	48	59.3	53	61.6	101	60.5
IIIB	33	40.7	33	38.4	66	39.5
Histology						
Non-Squamous cell carcinoma	40	49.4	49	57.0	89	53.3
Squamous cell carcinoma	41	50.6	37	43.0	78	46.7
Consented to tissue/blood collection						
No	22	27.2	17	19.8	39	23.4
Yes	59	72.8	69	80.2	128	76.6
Total	81	100.0	86	100.0	167	100.0

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

Table 4
Distribution of NRG-LU001 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	No Metformin (n=79)					Metformin (n=83)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	2 (2.5)	10 (12.7)	43 (54.4)	17 (21.5)	4 (5.1)	1 (1.2)	15 (18.1)	41 (49.4)	21 (25.3)	1 (1.2)
Blood and lymphatic system disorders	21 (26.6)	16 (20.3)	13 (16.5)	1 (1.3)	0 (0.0)	27 (32.5)	16 (19.3)	6 (7.2)	0 (0.0)	0 (0.0)
Cardiac disorders	3 (3.8)	6 (7.6)	1 (1.3)	1 (1.3)	0 (0.0)	9 (10.8)	8 (9.6)	4 (4.8)	1 (1.2)	0 (0.0)
Ear and labyrinth disorders	6 (7.6)	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	3 (3.8)	2 (2.5)	1 (1.3)	0 (0.0)	0 (0.0)	6 (7.2)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	18 (22.8)	34 (43.0)	13 (16.5)	0 (0.0)	0 (0.0)	13 (15.7)	45 (54.2)	14 (16.9)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	21 (26.6)	38 (48.1)	9 (11.4)	0 (0.0)	2 (2.5)	23 (27.7)	41 (49.4)	7 (8.4)	1 (1.2)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	1 (1.3)	25 (31.6)	12 (15.2)	2 (2.5)	0 (0.0)	2 (2.4)	14 (16.9)	12 (14.5)	2 (2.4)	0 (0.0)
Injury, poisoning and procedural complications	10 (12.7)	7 (8.9)	4 (5.1)	0 (0.0)	0 (0.0)	16 (19.3)	11 (13.3)	3 (3.6)	0 (0.0)	0 (0.0)
Investigations	5 (6.3)	7 (8.9)	29 (36.7)	13 (16.5)	0 (0.0)	10 (12.0)	12 (14.5)	24 (28.9)	14 (16.9)	0 (0.0)
Metabolism and nutrition disorders	17 (21.5)	24 (30.4)	8 (10.1)	3 (3.8)	0 (0.0)	17 (20.5)	23 (27.7)	16 (19.3)	3 (3.6)	0 (0.0)
Musculoskeletal and connective tissue disorders	18 (22.8)	23 (29.1)	3 (3.8)	0 (0.0)	0 (0.0)	23 (27.7)	24 (28.9)	4 (4.8)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1	1	0	1	0	0	0	1	0

Table 4
Distribution of NRG-LU001 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	No Metformin (n=79)					Metformin (n=83)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
	(0.0)	(1.3)	(1.3)	(0.0)	(1.3)	(0.0)	(0.0)	(0.0)	(1.2)	(0.0)
Nervous system disorders	21	25	8	1	0	27	19	13	0	0
	(26.6)	(31.6)	(10.1)	(1.3)	(0.0)	(32.5)	(22.9)	(15.7)	(0.0)	(0.0)
Psychiatric disorders	11	14	2	0	0	17	11	0	0	0
	(13.9)	(17.7)	(2.5)	(0.0)	(0.0)	(20.5)	(13.3)	(0.0)	(0.0)	(0.0)
Renal and urinary disorders	7	3	0	0	0	9	6	0	0	0
	(8.9)	(3.8)	(0.0)	(0.0)	(0.0)	(10.8)	(7.2)	(0.0)	(0.0)	(0.0)
Reproductive system and breast disorders	1	1	0	0	0	2	1	0	0	0
	(1.3)	(1.3)	(0.0)	(0.0)	(0.0)	(2.4)	(1.2)	(0.0)	(0.0)	(0.0)
Respiratory, thoracic and mediastinal disorders	15	27	16	3	1	15	25	13	4	1
	(19.0)	(34.2)	(20.3)	(3.8)	(1.3)	(18.1)	(30.1)	(15.7)	(4.8)	(1.2)
Skin and subcutaneous tissue disorders	22	20	1	0	0	16	25	1	0	0
	(27.8)	(25.3)	(1.3)	(0.0)	(0.0)	(19.3)	(30.1)	(1.2)	(0.0)	(0.0)
Vascular disorders	5	16	3	1	0	8	14	10	0	0
	(6.3)	(20.3)	(3.8)	(1.3)	(0.0)	(9.6)	(16.9)	(12.0)	(0.0)	(0.0)

Adverse events were graded with CTCAE version 4.

Table 5
Distribution of NRG-LU001 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	No Metformin (n=79)					Metformin (n=83)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
BLOOD AND LYMPHATIC SYSTEM DISORDERS	21	16	13	1	0	27	16	6	0	0
	(26.6)	(20.3)	(16.5)	(1.3)	(0.0)	(32.5)	(19.3)	(7.2)	(0.0)	(0.0)
Febrile neutropenia	0	0	4	1	0	0	0	0	0	0
	(0.0)	(0.0)	(5.1)	(1.3)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
CARDIAC DISORDERS	3	6	1	1	0	9	8	4	1	0
	(3.8)	(7.6)	(1.3)	(1.3)	(0.0)	(10.8)	(9.6)	(4.8)	(1.2)	(0.0)
Cardiac arrest	0	0	0	0	0	0	0	0	1	0
	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(1.2)	(0.0)
Heart failure	0	0	0	1	0	0	0	0	0	0
	(0.0)	(0.0)	(0.0)	(1.3)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)

Table 5
Distribution of NRG-LU001 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	No Metformin (n=79)					Metformin (n=83)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
EAR AND LABYRINTH DISORDERS	6 (7.6)	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hearing impaired	4 (5.1)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	21 (26.6)	38 (48.1)	9 (11.4)	0 (0.0)	2 (2.5)	23 (27.7)	41 (49.4)	7 (8.4)	1 (1.2)	0 (0.0)
Death NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion related reaction	1 (1.3)	3 (3.8)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.2)	0 (0.0)	1 (1.2)	0 (0.0)
INFECTIONS AND INFESTATIONS	1 (1.3)	25 (31.6)	12 (15.2)	2 (2.5)	0 (0.0)	2 (2.4)	14 (16.9)	12 (14.5)	2 (2.4)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)
INVESTIGATIONS	5 (6.3)	7 (8.9)	29 (36.7)	13 (16.5)	0 (0.0)	10 (12.0)	12 (14.5)	24 (28.9)	14 (16.9)	0 (0.0)
Lymphocyte count decreased	2 (2.5)	5 (6.3)	21 (26.6)	7 (8.9)	0 (0.0)	1 (1.2)	5 (6.0)	18 (21.7)	9 (10.8)	0 (0.0)
Neutrophil count decreased	5 (6.3)	5 (6.3)	7 (8.9)	6 (7.6)	0 (0.0)	8 (9.6)	10 (12.0)	10 (12.0)	4 (4.8)	0 (0.0)
Platelet count decreased	24 (30.4)	7 (8.9)	4 (5.1)	1 (1.3)	0 (0.0)	24 (28.9)	7 (8.4)	4 (4.8)	2 (2.4)	0 (0.0)
White blood cell decreased	9 (11.4)	16 (20.3)	11 (13.9)	5 (6.3)	0 (0.0)	9 (10.8)	13 (15.7)	15 (18.1)	3 (3.6)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	17 (21.5)	24 (30.4)	8 (10.1)	3 (3.8)	0 (0.0)	17 (20.5)	23 (27.7)	16 (19.3)	3 (3.6)	0 (0.0)
Dehydration	2 (2.5)	10 (12.7)	2 (2.5)	1 (1.3)	0 (0.0)	2 (2.4)	11 (13.3)	5 (6.0)	0 (0.0)	0 (0.0)
Hypernatremia	4 (5.1)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Hypocalcemia	7 (8.9)	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.2)	3 (3.6)	0 (0.0)	1 (1.2)	0 (0.0)
Hypokalemia	11 (13.9)	0 (0.0)	1 (1.3)	2 (2.5)	0 (0.0)	11 (13.3)	1 (1.2)	4 (4.8)	0 (0.0)	0 (0.0)

Table 5
Distribution of NRG-LU001 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	No Metformin (n=79)					Metformin (n=83)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Hyponatremia	11 (13.9)	0 (0.0)	4 (5.1)	0 (0.0)	0 (0.0)	17 (20.5)	0 (0.0)	6 (7.2)	1 (1.2)	0 (0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	1 (1.3)	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Myelodysplastic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other	0 (0.0)	1 (1.3)	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS	21 (26.6)	25 (31.6)	8 (10.1)	1 (1.3)	0 (0.0)	27 (32.5)	19 (22.9)	13 (15.7)	0 (0.0)	0 (0.0)
Intracranial hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	15 (19.0)	27 (34.2)	16 (20.3)	3 (3.8)	1 (1.3)	15 (18.1)	25 (30.1)	13 (15.7)	4 (4.8)	1 (1.2)
Aspiration	0 (0.0)	1 (1.3)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)
Dyspnea	13 (16.5)	23 (29.1)	5 (6.3)	2 (2.5)	0 (0.0)	21 (25.3)	11 (13.3)	10 (12.0)	2 (2.4)	0 (0.0)
Hypoxia	0 (0.0)	6 (7.6)	5 (6.3)	1 (1.3)	0 (0.0)	0 (0.0)	2 (2.4)	4 (4.8)	1 (1.2)	0 (0.0)
Pneumonitis	3 (3.8)	11 (13.9)	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	12 (14.5)	1 (1.2)	1 (1.2)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)
VASCULAR DISORDERS	5 (6.3)	16 (20.3)	3 (3.8)	1 (1.3)	0 (0.0)	8 (9.6)	14 (16.9)	10 (12.0)	0 (0.0)	0 (0.0)
Hypotension	3 (3.8)	7 (8.9)	0 (0.0)	1 (1.3)	0 (0.0)	2 (2.4)	5 (6.0)	4 (4.8)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 4.
Only includes system organ classes and terms with at least one Grade 4 or Grade 5.

Figure 1
Cumulative Accrual for NRG-LU001 – Data as of 04/30/2019