NRG-CC001

Report Based on Data Through: 03/14/2019

A Randomized Phase III Trial Of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients With Brain Metastases

STEP 1 REGISTRATION

STEP 2 RANDOMIZATION

Baseline neurocognitive assessment: HVLT-R, TMT, COWA ***(required)***

NOTE: Neurocognitive assessments can be uploaded at the time of Step 1 registration.

STRATIFICATION

RPA Class: (see Appendix III)

1. Class I
2. Class II

Prior therapy:

1. None
2. Radiosurgery or surgical resection*

Arm 1

WBRT 30 Gy/10 fractions
+
Memantine**

Arm 2

WBRT with Hippocampal Avoidance using IMRT 30 Gy/10 fractions
+
Memantine**

*Radiosurgery or surgical resection within 8 weeks of Step 1 registration; otherwise stratify to None.

**Memantine to be administered during and after WBRT or WBRT with hippocampal avoidance for a total of 24 weeks.

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Activated:	07/13/2015	
Closed:	03/12/2018	
Status:	Follow-up, primary endpoint published	

- **Study Description**
  This randomized phase III trial compares memantine hydrochloride and whole-brain radiotherapy (WBRT) with or without hippocampal avoidance in reducing neurocognitive decline in patients with cancer that has spread to the brain. Patients must have pathologically (histologically or cytologically) proven diagnosis of solid brain tumor within 5 years, be 18 years of age or older, speak English or French, and have a Karnofsky Performance Status of at least 70. The primary objective is to determine whether the addition of HA-WBRT increases time to neurocognitive failure as measured by neurocognitive decline on a battery of tests: the Hopkins Verbal Learning Test-Revised (HVLT-R) for Total Recall, Delayed Recall, and Delayed Recognition, Controlled Oral Word Association (COWA), and the Trail Making Test (TMT) Parts A and B.

- **Patient Accrual**
  Accrual was activated on July 13, 2015 and completed on March 12, 2018 with 518 patients randomized (Table 1). The median time of follow-up for vital status is 5 months.

- **Adverse Events**
  Adverse events (AEs) are graded with CTCAE version 4. AEs by system organ class are shown in Table 5. As of March 14, 2019, there have been 92 patients (39.7%) with grade 3, 21 patients (9.1%) with grade 4, and 30 patients (12.9%) with grade 5 events reported on the WBRT+Memantine arm compared to 72 patients (32.4%) with grade 3, 25 patients (11.3%) with grade 4, and 32 patients (14.4%) with grade 5 events reported on the HA-WBRT+Memantine arm regardless of attribution to treatment (Table 5). A notable difference exists for respiratory, thoracic and mediastinal disorders with the WBRT+Memantine arm having 15 (6.5%) grade 3+ events and the HA-WBRT+Memantine arm having 30 (13.6%) grade 3+ events. Table 6 shows the distribution of patients by highest grade AE and by specific AE term without regard to attribution. This table only includes system organ classes and terms with at least one grade 4 or 5 event. Most grade 5 events are Neoplasms benign,

malignant and unspecified (incl cysts and polyps) – Other with 13 on the WBRT+Memantine arm and 11 on the HA-WBRT+Memantine arm.

Table 1
NRG CC001 Accrual/Eligibility - Data as of 03/14/2019

	WBRT+Memantine	HA-WBRT+Memantine	Total
Screened	-	-	561
Randomized	257	261	518
Ineligible	32	30	62
Eligible	225	231	456

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

Table 2
Distribution of NRG-CC001 Patients by Highest Grade Adverse Event
by System Organ Class - Data as of 03/14/2019
For All Reported Adverse Events without Regard to Attribution

System Organ Class	WBRT+Memantine (n=232) n and (%) of Patients by Grade					HA-WBRT+Memantine (n=222) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	20 (8.6)	67 (28.9)	92 (39.7)	21 (9.1)	30 (12.9)	19 (8.6)	72 (32.4)	72 (32.4)	25 (11.3)	32 (14.4)
Blood and lymphatic system disorders	21 (9.1)	13 (5.6)	11 (4.7)	1 (0.4)	0 (0.0)	28 (12.6)	10 (4.5)	12 (5.4)	1 (0.5)	1 (0.5)
Cardiac disorders	9 (3.9)	6 (2.6)	6 (2.6)	2 (0.9)	0 (0.0)	8 (3.6)	8 (3.6)	3 (1.4)	1 (0.5)	0 (0.0)
Ear and labyrinth disorders	23 (9.9)	12 (5.2)	1 (0.4)	0 (0.0)	0 (0.0)	18 (8.1)	7 (3.2)	1 (0.5)	0 (0.0)	0 (0.0)
Endocrine disorders	5 (2.2)	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)	7 (3.2)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Eye disorders	34 (14.7)	14 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (14.0)	5 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	70 (30.2)	62 (26.7)	22 (9.5)	2 (0.9)	1 (0.4)	67 (30.2)	51 (23.0)	16 (7.2)	1 (0.5)	0 (0.0)
General disorders and administration site conditions	61 (26.3)	86 (37.1)	25 (10.8)	0 (0.0)	7 (3.0)	50 (22.5)	78 (35.1)	29 (13.1)	1 (0.5)	9 (4.1)
Hepatobiliary disorders	2 (0.9)	1 (0.4)	4 (1.7)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)

Table 2
Distribution of NRG-CC001 Patients by Highest Grade Adverse Event
by System Organ Class - Data as of 03/14/2019
For All Reported Adverse Events without Regard to Attribution

System Organ Class	WBRT+Memantine (n=232) n and (%) of Patients by Grade					HA-WBRT+Memantine (n=222) n and (%) of Patients by Grade				
	1	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Immune system disorders	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Infections and infestations	3 (1.3)	15 (6.5)	14 (6.0)	7 (3.0)	4 (1.7)	3 (1.4)	30 (13.5)	15 (6.8)	6 (2.7)	3 (1.4)
Injury, poisoning and procedural complications	22 (9.5)	13 (5.6)	5 (2.2)	0 (0.0)	0 (0.0)	25 (11.3)	4 (1.8)	7 (3.2)	0 (0.0)	0 (0.0)
Investigations	27 (11.6)	19 (8.2)	22 (9.5)	5 (2.2)	0 (0.0)	21 (9.5)	34 (15.3)	14 (6.3)	8 (3.6)	1 (0.5)
Metabolism and nutrition disorders	40 (17.2)	27 (11.6)	19 (8.2)	9 (3.9)	1 (0.4)	43 (19.4)	26 (11.7)	25 (11.3)	11 (5.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	44 (19.0)	41 (17.7)	26 (11.2)	0 (0.0)	0 (0.0)	23 (10.4)	48 (21.6)	24 (10.8)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (0.4)	2 (0.9)	1 (0.4)	13 (5.6)	0 (0.0)	1 (0.5)	4 (1.8)	0 (0.0)	11 (5.0)
Nervous system disorders	81 (34.9)	54 (23.3)	23 (9.9)	4 (1.7)	1 (0.4)	62 (27.9)	66 (29.7)	18 (8.1)	5 (2.3)	2 (0.9)
Psychiatric disorders	42 (18.1)	24 (10.3)	11 (4.7)	3 (1.3)	1 (0.4)	31 (14.0)	30 (13.5)	10 (4.5)	0 (0.0)	1 (0.5)
Renal and urinary disorders	16 (6.9)	9 (3.9)	2 (0.9)	0 (0.0)	1 (0.4)	10 (4.5)	7 (3.2)	5 (2.3)	0 (0.0)	1 (0.5)
Reproductive system and breast disorders	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	47 (20.3)	29 (12.5)	12 (5.2)	1 (0.4)	2 (0.9)	40 (18.0)	24 (10.8)	21 (9.5)	4 (1.8)	5 (2.3)
Skin and subcutaneous tissue disorders	43 (18.5)	47 (20.3)	4 (1.7)	1 (0.4)	0 (0.0)	29 (13.1)	45 (20.3)	1 (0.5)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)
Vascular disorders	8 (3.4)	11 (4.7)	23 (9.9)	2 (0.9)	0 (0.0)	8 (3.6)	11 (5.0)	25 (11.3)	5 (2.3)	0 (0.0)

Adverse events were graded with CTCAE version 4.0.

Table 3
Distribution of NRG-CC001 Patients by Highest Grade Adverse Event
by Specific Adverse Event Term - Data as of 03/14/2019
For Selected Adverse Events without Regard to Attribution

System Organ Class/Term	WBRT+Memantine (n=232) n and (%) of Patients by Grade					HA-WBRT+Memantine (n=222) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
BLOOD AND LYMPHATIC SYSTEM DISORDERS	21 (9.1)	13 (5.6)	11 (4.7)	1 (0.4)	0 (0.0)	28 (12.6)	10 (4.5)	12 (5.4)	1 (0.5)	1 (0.5)
Anemia	22 (9.5)	10 (4.3)	7 (3.0)	1 (0.4)	0 (0.0)	27 (12.2)	11 (5.0)	9 (4.1)	0 (0.0)	1 (0.5)
Febrile neutropenia	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
CARDIAC DISORDERS	9 (3.9)	6 (2.6)	6 (2.6)	2 (0.9)	0 (0.0)	8 (3.6)	8 (3.6)	3 (1.4)	1 (0.5)	0 (0.0)
Cardiac disorders - Other	2 (0.9)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Pericardial effusion	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Pericardial tamponade	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 (0.5)	0 (0.0)
GASTROINTESTINAL DISORDERS	70 (30.2)	62 (26.7)	22 (9.5)	2 (0.9)	1 (0.4)	67 (30.2)	51 (23.0)	16 (7.2)	1 (0.5)	0 (0.0)
Colitis	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	0 (0.0)
Constipation	37 (15.9)	21 (9.1)	2 (0.9)	1 (0.4)	0 (0.0)	30 (13.5)	11 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Small intestinal perforation	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	61 (26.3)	86 (37.1)	25 (10.8)	0 (0.0)	7 (3.0)	50 (22.5)	78 (35.1)	29 (13.1)	1 (0.5)	9 (4.1)
Death NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.6)
General disorders and administration site conditions - Other	4 (1.7)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	5 (2.3)	2 (0.9)	3 (1.4)	0 (0.0)	1 (0.5)
Multi-organ failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

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	1	2	3	4	5	1	2	3	4	5
Sudden death NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
HEPATOBILIARY DISORDERS	2 (0.9)	1 (0.4)	4 (1.7)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Hepatic 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)	0 (0.0)	1 (0.5)
INFECTIONS AND INFESTATIONS	3 (1.3)	15 (6.5)	14 (6.0)	7 (3.0)	4 (1.7)	3 (1.4)	30 (13.5)	15 (6.8)	6 (2.7)	3 (1.4)
Abdominal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Encephalitis infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations - Other	0 (0.0)	1 (0.4)	4 (1.7)	0 (0.0)	1 (0.4)	1 (0.5)	8 (3.6)	2 (0.9)	0 (0.0)	0 (0.0)
Lung infection	0 (0.0)	2 (0.9)	8 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	6 (2.7)	1 (0.5)	2 (0.9)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.4)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.7)	1 (0.5)
INVESTIGATIONS	27 (11.6)	19 (8.2)	22 (9.5)	5 (2.2)	0 (0.0)	21 (9.5)	34 (15.3)	14 (6.3)	8 (3.6)	1 (0.5)
Blood bilirubin increased	1 (0.4)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.8)	1 (0.5)	1 (0.5)	0 (0.0)
Investigations - Other	4 (1.7)	1 (0.4)	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)
Lymphocyte count decreased	5 (2.2)	5 (2.2)	8 (3.4)	4 (1.7)	0 (0.0)	9 (4.1)	9 (4.1)	4 (1.8)	3 (1.4)	0 (0.0)
Neutrophil count decreased	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.7)	0 (0.0)	1 (0.5)	3 (1.4)	0 (0.0)
Platelet count decreased	8 (3.4)	6 (2.6)	2 (0.9)	1 (0.4)	0 (0.0)	11 (5.0)	3 (1.4)	2 (0.9)	3 (1.4)	0 (0.0)
White blood cell decreased	8 (3.4)	2 (0.9)	3 (1.3)	0 (0.0)	0 (0.0)	10 (4.5)	8 (3.6)	2 (0.9)	2 (0.9)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	40 (17.2)	27 (11.6)	19 (8.2)	9 (3.9)	1 (0.4)	43 (19.4)	26 (11.7)	25 (11.3)	11 (5.0)	0 (0.0)

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For Selected Adverse Events without Regard to Attribution

System Organ Class/Term	WBRT+Memantine (n=232) n and (%) of Patients by Grade					HA-WBRT+Memantine (n=222) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Anorexia	39 (16.8)	26 (11.2)	7 (3.0)	1 (0.4)	0 (0.0)	36 (16.2)	29 (13.1)	5 (2.3)	0 (0.0)	0 (0.0)
Dehydration	6 (2.6)	7 (3.0)	2 (0.9)	0 (0.0)	0 (0.0)	5 (2.3)	6 (2.7)	8 (3.6)	1 (0.5)	0 (0.0)
Hypercalcemia	2 (0.9)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Hyperglycemia	7 (3.0)	3 (1.3)	4 (1.7)	3 (1.3)	0 (0.0)	13 (5.9)	3 (1.4)	4 (1.8)	1 (0.5)	0 (0.0)
Hypoalbuminemia	12 (5.2)	4 (1.7)	4 (1.7)	0 (0.0)	0 (0.0)	9 (4.1)	6 (2.7)	2 (0.9)	1 (0.5)	0 (0.0)
Hypocalcemia	10 (4.3)	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	3 (1.4)	1 (0.5)	1 (0.5)	0 (0.0)
Hypoglycemia	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.8)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Hypokalemia	11 (4.7)	6 (2.6)	3 (1.3)	2 (0.9)	0 (0.0)	12 (5.4)	3 (1.4)	4 (1.8)	1 (0.5)	0 (0.0)
Hyponatremia	15 (6.5)	0 (0.0)	5 (2.2)	3 (1.3)	0 (0.0)	11 (5.0)	0 (0.0)	6 (2.7)	3 (1.4)	0 (0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	1 (0.4)	2 (0.9)	1 (0.4)	13 (5.6)	0 (0.0)	1 (0.5)	4 (1.8)	0 (0.0)	11 (5.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	13 (5.6)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	11 (5.0)
NERVOUS SYSTEM DISORDERS	81 (34.9)	54 (23.3)	23 (9.9)	4 (1.7)	1 (0.4)	62 (27.9)	66 (29.7)	18 (8.1)	5 (2.3)	2 (0.9)
Edema cerebral	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Intracranial hemorrhage	2 (0.9)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)
Nervous system disorders - Other	8 (3.4)	7 (3.0)	1 (0.4)	0 (0.0)	1 (0.4)	3 (1.4)	1 (0.5)	3 (1.4)	0 (0.0)	0 (0.0)
Peripheral motor neuropathy	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	1 (0.5)	0 (0.0)

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by Specific Adverse Event Term - Data as of 03/14/2019
For Selected Adverse Events without Regard to Attribution

System Organ Class/Term	WBRT+Memantine (n=232) n and (%) of Patients by Grade					HA-WBRT+Memantine (n=222) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Seizure	5 (2.2)	10 (4.3)	7 (3.0)	1 (0.4)	0 (0.0)	3 (1.4)	4 (1.8)	2 (0.9)	0 (0.0)	0 (0.0)
Somnolence	3 (1.3)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.9)	1 (0.5)	0 (0.0)	1 (0.5)
Stroke	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
PSYCHIATRIC DISORDERS	42 (18.1)	24 (10.3)	11 (4.7)	3 (1.3)	1 (0.4)	31 (14.0)	30 (13.5)	10 (4.5)	0 (0.0)	1 (0.5)
Confusion	11 (4.7)	12 (5.2)	7 (3.0)	1 (0.4)	0 (0.0)	16 (7.2)	10 (4.5)	6 (2.7)	0 (0.0)	0 (0.0)
Delirium	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.5)	4 (1.8)	2 (0.9)	0 (0.0)	0 (0.0)
Psychiatric disorders - Other	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.5)	2 (0.9)	1 (0.5)	0 (0.0)	1 (0.5)
Suicidal ideation	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	0 (0.0)	0 (0.0)
RENAL AND URINARY DISORDERS	16 (6.9)	9 (3.9)	2 (0.9)	0 (0.0)	1 (0.4)	10 (4.5)	7 (3.2)	5 (2.3)	0 (0.0)	1 (0.5)
Acute kidney injury	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	3 (1.4)	0 (0.0)	3 (1.4)	0 (0.0)	1 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	47 (20.3)	29 (12.5)	12 (5.2)	1 (0.4)	2 (0.9)	40 (18.0)	24 (10.8)	21 (9.5)	4 (1.8)	5 (2.3)
Aspiration	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Dyspnea	27 (11.6)	17 (7.3)	7 (3.0)	1 (0.4)	1 (0.4)	26 (11.7)	16 (7.2)	15 (6.8)	2 (0.9)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	43 (18.5)	47 (20.3)	4 (1.7)	1 (0.4)	0 (0.0)	29 (13.1)	45 (20.3)	1 (0.5)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders - Other	7 (3.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)	8 (3.6)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
VASCULAR DISORDERS	8 (3.4)	11 (4.7)	23 (9.9)	2 (0.9)	0 (0.0)	8 (3.6)	11 (5.0)	25 (11.3)	5 (2.3)	0 (0.0)

Table 3
Distribution of NRG-CC001 Patients by Highest Grade Adverse Event
by Specific Adverse Event Term - Data as of 03/14/2019
For Selected Adverse Events without Regard to Attribution

System Organ Class/Term	WBRT+Memantine (n=232) n and (%) of Patients by Grade					HA-WBRT+Memantine (n=222) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Thromboembolic event	0 (0.0)	7 (3.0)	13 (5.6)	2 (0.9)	0 (0.0)	0 (0.0)	3 (1.4)	14 (6.3)	5 (2.3)	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 5.