RTOG 1308

Report Based on Data Through: 04/30/2019

Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC

S T R A T I F Y	**Stage** 1. II/IIIA 2. IIIB **Histology** 1. Squamous 2. Non-Squamous **Concurrent Chemotherapy Doublet Type** 1. Carboplatin/paclitaxel or carboplatin/pemetrexed (non-squamous cell carcinoma only) 2. Cisplatin/etoposide **Planned Use of Immunotherapy** 1. Yes 2. No	**R A N D O M I Z E**	**Arm 1**: Photon dose—70 Gy*(RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy** **Arm 2**: Proton dose—70 Gy (RBE), at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**	**Both Arms**: Standard of Care Consolidation Systemic Treatment per treating physician ***

*The total prescribed dose will be 70 Gy [Relative Biological Effectiveness (RBE)] **without exceeding tolerance dose-volume limits of all critical normal structures**. (See Section 6.1.3 when 70 Gy (RBE) is not achieved.)

**Chemotherapy delivered concurrently, cisplatin/ etoposide or carboplatin/paclitaxel, or carboplatin/pemetrexed doublets, is required. The site/investigator must declare the chemotherapy regimen that the patient will receive prior to the patient's randomization. See Section 7.0 for details.

*** Standard of Care Consolidation systemic treatment per treating physician. Consolidation immunotherapy with durvalumab may be given per treating physician after the completion of radiotherapy. If durvalumab is given, patients do not require any further consolidation chemotherapy after radiotherapy is completed. If consolidation durvalumab is NOT given, the following patients require further systemic therapy after the completion of radiotherapy:

Patients who receive concurrent weekly carboplatin/paclitaxel are required to receive 2 cycles of consolidation carboplatin/paclitaxel.

Patients who receive concurrent carboplatin/pemetrexed (non-squamous cell carcinoma only) are required to receive a total of 4 cycles of carboplatin/pemetrexed. These patients therefore will receive cycle #4 of carboplatin/pemetrexed after the completion of radiotherapy. If cycle #3 is delayed, it is possible that it will also be received after the completion of radiotherapy.

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Activated:	02/03/2014	
Status:	Accruing	

- **Study Description**
  This is a two-armed randomized phase III study designed to assess whether proton therapy will improve the rate of overall survival and decrease the rate of treatment-related cardiac toxicity and lymphopenia as compared to standard photon therapy for patients with inoperable stage IIIA or IIIB locally advanced non-small cell lung cancer. The co-primary endpoints are overall survival and treatment-related cardiac toxicity/lymphocyte reduction. Amendment 3 which addressed the slower than anticipated accrual was broadcast on February 20, 2018. In addition to adding a co-primary enpdoint of treatment-related cardiac toxicity and lymphocyte reduction, the study's redesign also included a reduction in the overall sample size from 560 to 330 patients, and the anticipated monthly accrual rate was adjusted to 6-7 patients a month to better reflect the slower-than-expected accrual. Please refer to the protocol's summary of changes on the CTSU website for additional details.

- **Patient Accrual**
  Accrual was activated on February 3, 2014. Total accrual as of April 30, 2019, is 151 (Table 1). Monthly accrual is slower than anticipated, in part due to refusal by some medical insurers to cover the cost of proton therapy. As of April 30, 2019, the median time of follow-up for vital status is 18.6 months. A planned interim analysis for futility/inferiority is projected to occur in summer 2021.

- **Patient and Tumor Characteristics**
  One patient on Photon Therapy and five patients on Proton Therapy are ineligible for analysis (Table 2). The distribution by patient and tumor characteristics is shown in Table 3. Median (min-max) age is 68 years (43-82). Most patients are male (60.0%), white (79.3%), not Hispanic or Latino (93.1%), and had a Zubrod

Performance Status of 0 (47.6%) As of April 30, 2019, 7 patients on Photon Therapy and 9 patients on Proton Therapy have withdrawn consent to follow-up.

- **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 4 (6.6%) patients with grade 4 and 4 (6.6%) patients with grade 5 AEs reported on Photon Therapy, and 9 (14.8%) patients with grade 4 and 1 (1.6%) patients with grade 5 AEs reported on Proton 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 Photon arm (death NOS, definitely related to treatment), and a new incidence of grade 5 AE reported in Proton arm (sudden death NOS, unrelated to treatment). There are no notable differences in grade 4-5 rates by term.

Table 1
RTOG 1308 Accrual Summary - Data as of 04/30/2019

Date activated to accrual:	February 3, 2014
Targeted sample size:	330
Projected monthly accrual*:	6-7
Average monthly accrual over last 6 months:	3.0
Projected accrual as of 04/30/2019:	197
Total accrual as of 04/30/2019:	151
Percent of projected accrual achieved as of 04/30/2019:	76.65%
Percent of total targeted accrual as of 04/30/2019:	45.76%
Projected completion date based on last 6 months accrual:	April 2024

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

Table 2
RTOG 1308 Accrual/Eligibility - Data as of 04/30/2019

	Photon Therapy	**Proton Therapy**	**Total**
Randomized	74	77	151
Ineligible	1	5	6
Eligible	73	72	145

Table 3
Patient and Tumor Characteristics for All Eligible Patients in RTOG 1308 - Data as of 04/30/2019

	Photon Therapy		Proton Therapy		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age (years)						
≤ 49	2	2.7	2	2.8	4	2.8
50 - 59	14	19.2	11	15.3	25	17.2
60 - 69	22	30.1	26	36.1	48	33.1
≥ 70	35	47.9	33	45.8	68	46.9
Gender						
Male	45	61.6	42	58.3	87	60.0
Female	28	38.4	30	41.7	58	40.0
Race						
Asian	1	1.4	2	2.8	3	2.1
Black or African American	12	16.4	7	9.7	19	13.1
Native Hawaiian or Other Pacific Islander	0	0.0	1	1.4	1	0.7
White	55	75.3	60	83.3	115	79.3
Unknown	5	6.8	2	2.8	7	4.8
Ethnicity						
Hispanic or Latino	2	2.7	0	0.0	2	1.4
Not Hispanic or Latino	67	91.8	68	94.4	135	93.1
Unknown	4	5.5	4	5.6	8	5.5
Zubrod Performance Status						
0	36	49.3	33	45.8	69	47.6
1	33	45.2	35	48.6	68	46.9
Pending	4	5.5	4	5.6	8	5.5
AJCC Stage*						
II	5	6.8	9	12.5	14	9.7
IIIA	42	57.5	40	55.6	82	56.6
IIIB	26	35.6	23	31.9	49	33.8
Histology*						
Non-Squamous cell carcinoma	43	58.9	39	54.2	82	56.6
Squamous cell carcinoma	30	41.1	33	45.8	63	43.4
Chemotherapy Regimen*						
Carboplatin and Paclitaxel	62	84.9	64	88.9	126	86.9
Carboplatin and Pemetrexed	3	4.1	2	2.8	5	3.4

Table 3
Patient and Tumor Characteristics for All Eligible Patients in
RTOG 1308 - Data as of 04/30/2019

	Photon Therapy		Proton Therapy		Total	
Patient or Tumor Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Cisplatin and Etoposide	8	11.0	6	8.3	14	9.7
Consented to PRO/QOL collection						
No	12	16.4	10	13.9	22	15.2
Yes	61	83.6	62	86.1	123	84.8
Consented to tissue collection						
No	48	65.8	43	59.7	91	62.8
Yes	25	34.2	29	40.3	54	37.2
Consented to blood collection						
No	52	71.2	46	63.9	98	67.6
Yes	21	28.8	26	36.1	47	32.4
Total	73	100.0	72	100.0	145	100.0

*Stratification factor

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

Table 4
Distribution of RTOG 1308 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

	Photon Therapy (n=61)					Proton Therapy (n=61)				
System Organ Class	**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	5 (8.2)	13 (21.3)	31 (50.8)	4 (6.6)	4 (6.6)	1 (1.6)	16 (26.2)	29 (47.5)	9 (14.8)	1 (1.6)
Blood and lymphatic system disorders	9 (14.8)	11 (18.0)	6 (9.8)	0 (0.0)	0 (0.0)	14 (23.0)	13 (21.3)	4 (6.6)	0 (0.0)	0 (0.0)
Cardiac disorders	3 (4.9)	2 (3.3)	4 (6.6)	1 (1.6)	0 (0.0)	7 (11.5)	2 (3.3)	1 (1.6)	1 (1.6)	0 (0.0)
Ear and labyrinth disorders	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	3 (4.9)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	10 (16.4)	33 (54.1)	8 (13.1)	0 (0.0)	0 (0.0)	17 (27.9)	31 (50.8)	5 (8.2)	1 (1.6)	0 (0.0)

Table 4
Distribution of RTOG 1308 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	Photon Therapy (n=61) n and (%) of Patients by Grade					Proton Therapy (n=61) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
General disorders and administration site conditions	21 (34.4)	23 (37.7)	4 (6.6)	0 (0.0)	1 (1.6)	12 (19.7)	33 (54.1)	6 (9.8)	0 (0.0)	1 (1.6)
Immune system disorders	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Infections and infestations	1 (1.6)	11 (18.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	11 (18.0)	7 (11.5)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	15 (24.6)	8 (13.1)	4 (6.6)	0 (0.0)	0 (0.0)	14 (23.0)	13 (21.3)	8 (13.1)	0 (0.0)	0 (0.0)
Investigations	6 (9.8)	12 (19.7)	11 (18.0)	4 (6.6)	0 (0.0)	6 (9.8)	10 (16.4)	10 (16.4)	5 (8.2)	0 (0.0)
Metabolism and nutrition disorders	8 (13.1)	13 (21.3)	6 (9.8)	0 (0.0)	0 (0.0)	12 (19.7)	15 (24.6)	7 (11.5)	2 (3.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	7 (11.5)	7 (11.5)	3 (4.9)	0 (0.0)	0 (0.0)	12 (19.7)	14 (23.0)	2 (3.3)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)
Nervous system disorders	19 (31.1)	5 (8.2)	6 (9.8)	0 (0.0)	0 (0.0)	11 (18.0)	12 (19.7)	1 (1.6)	0 (0.0)	0 (0.0)
Psychiatric disorders	11 (18.0)	4 (6.6)	2 (3.3)	0 (0.0)	0 (0.0)	18 (29.5)	2 (3.3)	1 (1.6)	0 (0.0)	0 (0.0)
Renal and urinary disorders	4 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	17 (27.9)	17 (27.9)	5 (8.2)	1 (1.6)	2 (3.3)	13 (21.3)	23 (37.7)	11 (18.0)	2 (3.3)	0 (0.0)
Skin and subcutaneous tissue disorders	13 (21.3)	6 (9.8)	1 (1.6)	0 (0.0)	0 (0.0)	12 (19.7)	7 (11.5)	1 (1.6)	0 (0.0)	0 (0.0)
Vascular disorders	2 (3.3)	3 (4.9)	5 (8.2)	1 (1.6)	0 (0.0)	5 (8.2)	3 (4.9)	6 (9.8)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 4.0.

Table 5
Distribution of RTOG 1308 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	Photon Therapy (n=61) n and (%) of Patients by Grade					Proton Therapy (n=61) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
CARDIAC DISORDERS	3 (4.9)	2 (3.3)	4 (6.6)	1 (1.6)	0 (0.0)	7 (11.5)	2 (3.3)	1 (1.6)	1 (1.6)	0 (0.0)
Atrial fibrillation	0 (0.0)	1 (1.6)	3 (4.9)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GASTROINTESTINAL DISORDERS	10 (16.4)	33 (54.1)	8 (13.1)	0 (0.0)	0 (0.0)	17 (27.9)	31 (50.8)	5 (8.2)	1 (1.6)	0 (0.0)
Esophageal ulcer	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.6)	0 (0.0)	1 (1.6)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	21 (34.4)	23 (37.7)	4 (6.6)	0 (0.0)	1 (1.6)	12 (19.7)	33 (54.1)	6 (9.8)	0 (0.0)	1 (1.6)
Death NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden death NOS	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 (1.6)
INFECTIONS AND INFESTATIONS	1 (1.6)	11 (18.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	11 (18.0)	7 (11.5)	0 (0.0)	0 (0.0)
Infections and infestations - Other	0 (0.0)	2 (3.3)	1 (1.6)	1 (1.6)	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
INVESTIGATIONS	6 (9.8)	12 (19.7)	11 (18.0)	4 (6.6)	0 (0.0)	6 (9.8)	10 (16.4)	10 (16.4)	5 (8.2)	0 (0.0)
Investigations - Other	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	2 (3.3)	5 (8.2)	1 (1.6)	0 (0.0)	1 (1.6)	3 (4.9)	5 (8.2)	4 (6.6)	0 (0.0)
Neutrophil count decreased	2 (3.3)	2 (3.3)	7 (11.5)	2 (3.3)	0 (0.0)	2 (3.3)	6 (9.8)	3 (4.9)	1 (1.6)	0 (0.0)
White blood cell decreased	6 (9.8)	9 (14.8)	4 (6.6)	2 (3.3)	0 (0.0)	7 (11.5)	5 (8.2)	5 (8.2)	1 (1.6)	0 (0.0)

Table 5
Distribution of RTOG 1308 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	Photon Therapy (n=61) n and (%) of Patients by Grade					Proton Therapy (n=61) n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
METABOLISM AND NUTRITION DISORDERS	8 (13.1)	13 (21.3)	6 (9.8)	0 (0.0)	0 (0.0)	12 (19.7)	15 (24.6)	7 (11.5)	2 (3.3)	0 (0.0)
Hyperglycemia	3 (4.9)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	3 (4.9)	1 (1.6)	0 (0.0)	2 (3.3)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	17 (27.9)	17 (27.9)	5 (8.2)	1 (1.6)	2 (3.3)	13 (21.3)	23 (37.7)	11 (18.0)	2 (3.3)	0 (0.0)
Bronchopulmonary hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)
Hypoxia	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.2)	2 (3.3)	1 (1.6)	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)	1 (1.6)	0 (0.0)
Respiratory, thoracic and mediastinal disorders - Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	3 (4.9)	1 (1.6)	2 (3.3)	0 (0.0)	0 (0.0)
VASCULAR DISORDERS	2 (3.3)	3 (4.9)	5 (8.2)	1 (1.6)	0 (0.0)	5 (8.2)	3 (4.9)	6 (9.8)	0 (0.0)	0 (0.0)
Hypotension	1 (1.6)	1 (1.6)	2 (3.3)	1 (1.6)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	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.
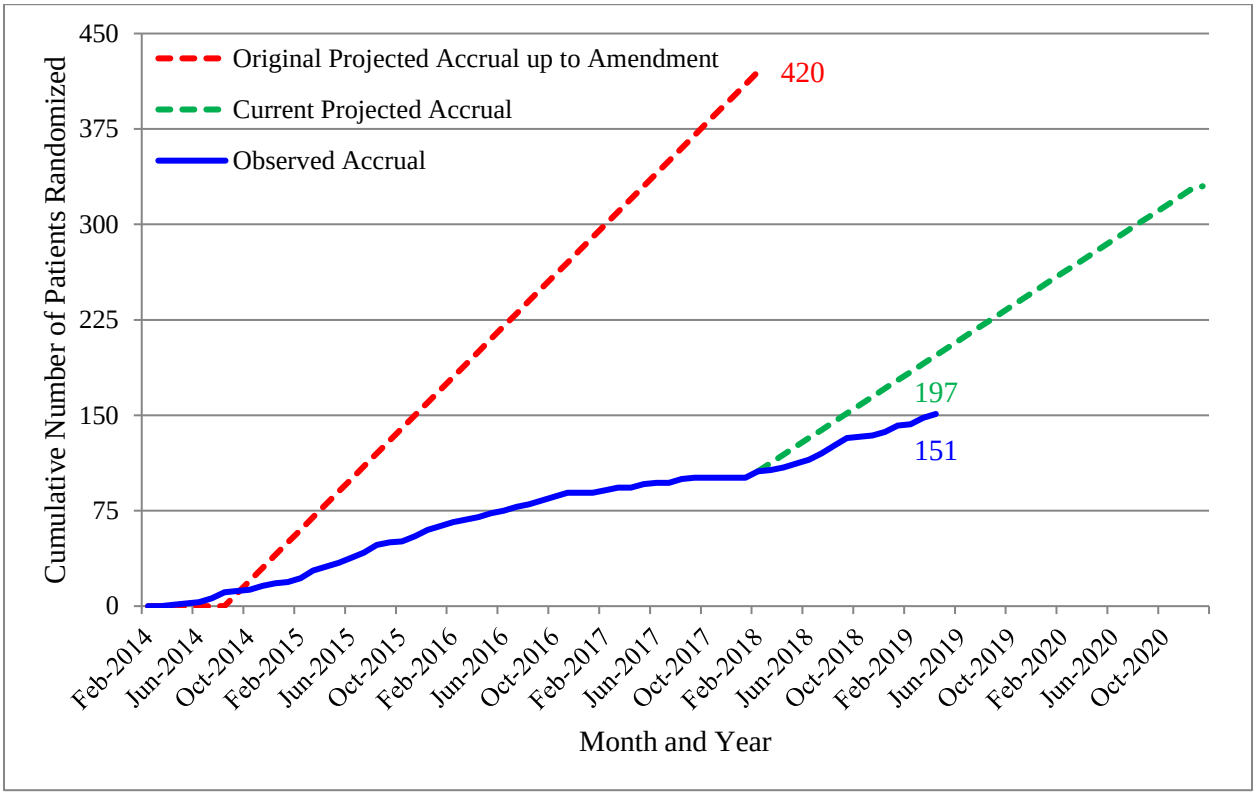
Figure 1
Cumulative Accrual for RTOG 1308 - Data as of 04/30/2019