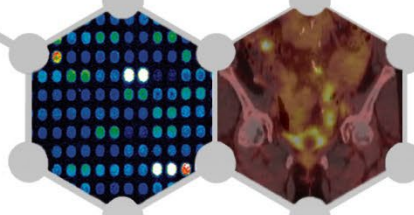

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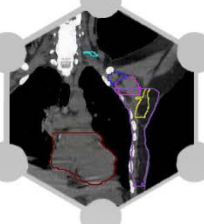

PHASE III RANDOMIZED TRIAL COMPARING OVERALL SURVIVAL AFTER PHOTON VERSUS PROTON CHEMORADIOTHERAPY FOR INOPERABLE STAGE II-IIIB NSCLC RTOG-1308

PI: Zhongxing, Liao, MD

NRG Oncology Semi-Annual Meeting
July 23, 2022

Co-Chairs

Study Chair: Zhongxing Liao, MD

Radiation Oncology:

Jeffrey Bradley, MD, Emory University

Charles Simone, MD, New York Proton Center

Quyhn Nguyen, MD, MD Anderson Cancer Center

Brad Hoppe, MD, Mayo Clinic Florida

Medical Oncology:

Charles Lu, MD, MD Anderson

Medical Physics:

Michael Gillin, PhD, MD Anderson

Radhe Mohan, PhD, MD Anderson

Translational Research: Steven H. Lin, MD, PhD, MD Anderson

Quality of Life: Xin Shelley Wang, MD, MD Anderson

Outcomes: Ben Movsas, MD, Henry Ford Health System

Comparative Cost Effectiveness:

Deborah Bruner, RN, PhD, Emory University

Gregory Russo, MD, Boston University School of Medicine

Statistics: Chen Hu, PhD

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Hypothesis

When standard constraints on radiation dose and volume to organs at risk (OARs) are used, proton beam therapy will allow lower doses to critical organs and higher doses to be delivered to the target compared with photons, which will result in an improvement of median survival time from 21 months (control arm) to 28 months (proton arm) in patients with good performance status and stage II-IIIB non-small cell lung cancer (NSCLC)

RTOG-1308

PRIMARY OBJECTIVE

- **To compare the overall survival (OS) in patients with stage II-IIIB NSCLC after image-guided, motion-managed photon radiotherapy (Arm 1) or after image-guided, motion-managed proton radiotherapy (Arm 2) both given with concurrent platinum-based chemotherapy**

- **To compare the cardiac toxicity and lymphopenia reduction (lymphopenia) definitely, probably, or possibly related to treatment between the 2 arms**

RTOG 1308 Schema

STRATIFY	RANDOMIZE		
Stage 1.II 2.IIIA 3.IIIB Histology 1.Squamous 2.Non-Squamous Concurrent Chemotherapy Doublet Type 1.Carboplatin/paclitaxel 2.Cisplatin/etoposide 3. carboplatin/ pemetrexed		Arm 1: Photon dose—70 Gy*, at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy** Arm 2: Proton dose—70 Gy (RBE), at 2 Gy once daily plus platinum-based doublet chemotherapy**	Both Arms: Durvalumab or Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***

*The highest total prescribed dose will be 70 Gy (Relative Biological Effectiveness (RBE)) **without exceeding tolerance dose-volume limits of all critical normal structures**. The dose range can be 60-70Gy provided the dose constraints of OARs are met.

** Chemotherapy delivered concurrently, cisplatin/ etoposide or carboplatin/paclitaxel, or carboplatin/ pemetrexed doublets, is required. Chemotherapy regimen must be declared prior to 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.

Study Endpoints with Hypotheses (Including PROs/CERs)

Primary Objectives:

1. Overall survival (OS)
2. Cardiac AE and lymphocyte reduction (lymphopenia)

Secondary Objectives:

1. 2-year progression-free survival (PFS)
2. Grade ≥3 other AEs (definitely, probably, or possibly related to treatment)
3. QOL: primarily on the development of **shortness of breath** at 6 ms; and secondarily on the development of **sore throat** at the end of chemoRT (as measured by the MDASI-Lung), and breathing related functioning impairments as measured by the Shortness Breath Questionnaire [SOBQ];
4. Cost-effectiveness outcomes
5. Pulmonary function changes by treatment arms and response;
6. The most appropriate and clinically relevant technological parameters to ensure quality and effectiveness throughout RT processes,

C›I›R›B
FOR THE NATIONAL CANCER INSTITUTE

CIRB Approval of Continuing Review

Date: May 6, 2022

Study ID: RTOG-1308

Study Title: Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy For Inoperable Stage II-IIIB NSCLC

Protocol Version Date: 10/06/21

Study Chair: Zhongxing Liao M.D.

At the convened meeting of the NCI Adult CIRB - Late Phase Emphasis held on May 5, 2022, the CIRB conducted its continuing review of RTOG-1308 and voted to approve for 12 months minus 1 day.

CIRB approval for this study will expire on May 4, 2023.

The following documents were reviewed:

1. CIRB Application (PVD 10/06/21)
2. Consent Form (PVD 10/06/21)
3. COVID-19 Deviation Report dated April 2022
4. Cumulative Inclusion Enrollment Report
5. DSMB Report dated 02/10/22
6. Protocol Version Date 10/06/21
7. Study Summary dated February 2022

As the Study Chair, you are responsible for reporting all study-related activity and correspondence to the CIRB.

The CIRB complies with the Federal regulations 45 CFR 46, 21 CFR 50, and 21 CFR 56.

If you have any questions regarding this review, please contact the Adult CIRB - Late Phase Emphasis Coordinator at adultcirb@emmes.com.

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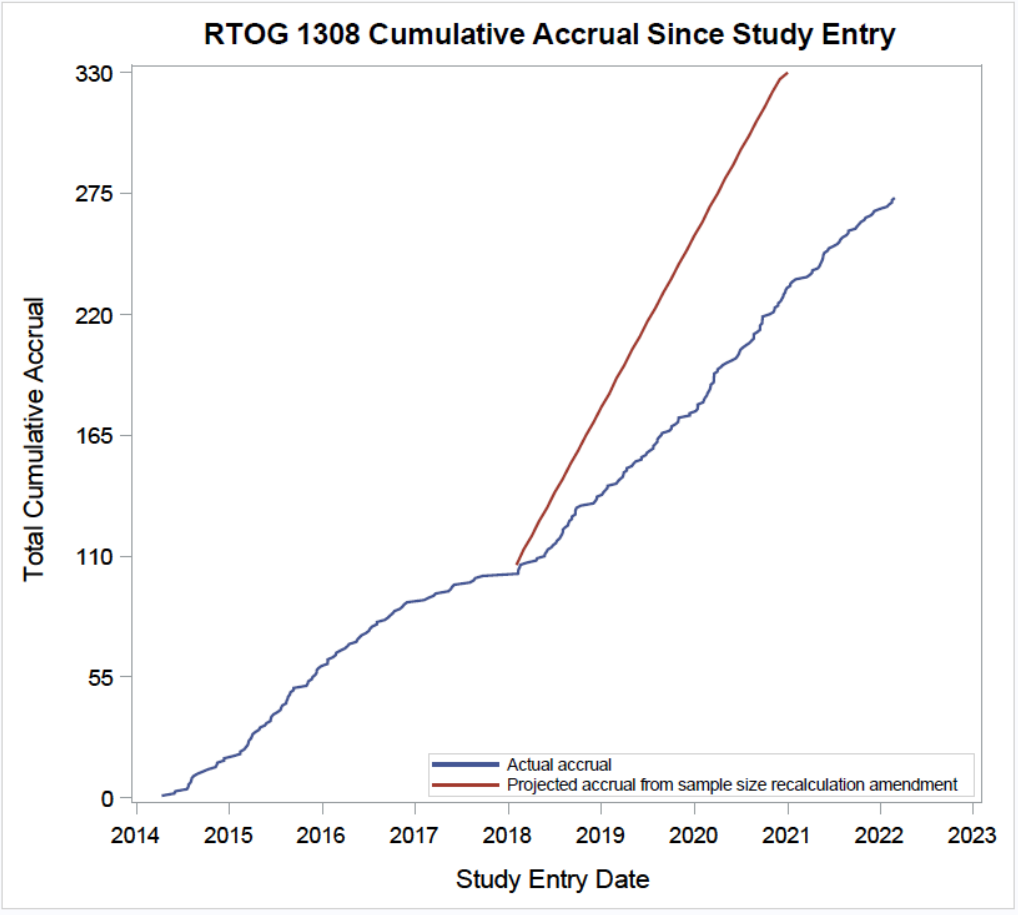
cc: Christina Freeman, CCRP
Fran Bradley BA
Jeffrey Bradley MD
Kathryn Okrent BA, Masters

Sites and Accrual: Total Accrual = 283/330
(through 7/10/2022)

RTOG 1308 Yearly Accrual	
Year	**Total Accrual**
2022	15*
2021	36
2020	57
2019	38
2018	36
2017	12
2016	29
2015	42
2014	18



Enrolled 35 pts since the 6/2021 amendment

Only 47 patients left to go!!

RTOG 1308: Total Accrual Through 2022-03-03 = 273

RTOG 1308 Accrual by Institution
Grouped by Main Member

Accrual Ranking	CTEP ID	Site	Accrual
1	**LAPS-TX035**	**University of Texas MD Anderson Cancer Center LAPS**	**107**
	TX035	M D Anderson Cancer Center	86
	TX400	MD Anderson West Houston	21
2	**FL078**	**Miami Cancer Institute**	**29**
	FL078	Miami Cancer Institute	29
3	**LAPS-MO011**	**Washington University - Siteman Cancer Center LAPS**	**25**
	MO011	Washington University School of Medicine	24
	MO053	Siteman Cancer Center at West County Hospital	1
	PA075	**University of Pennsylvania/Abramson Cancer Center**	**25**
	PA075	University of Pennsylvania/Abramson Cancer Center	25
4	**LAPS-NY016**	**Memorial Sloan-Kettering Cancer Center LAPS**	**17**
	NJ200	Memorial Sloan Kettering Basking Ridge	10
	NY016	Memorial Sloan Kettering Cancer Center	5
	NJ299	Memorial Sloan Kettering Monmouth	1
	NY478	Memorial Sloan Kettering Westchester	1
5	**FL015**	**University of Florida Health Science Center - Gainesville**	**10**
	FL005	University of Florida Health Science Center - Jacksonville	10
6	**IL387**	**Northwestern Medicine Cancer Center Warrenville**	**9**
	IL387	Northwestern Medicine Cancer Center Warrenville	9
7	**LAPS-MA036**	**Dana-Farber / Partners CancerCare LAPS**	**8**
	MA034	Massachusetts General Hospital Cancer Center	6
	MA093	Mass General/North Shore Cancer Center	2
	OH070	**University of Cincinnati/Barrett Cancer Center**	**8**
	OH394	University Pointe	8
8	**MD015**	**University of Maryland/Greenebaum Cancer Center**	**7**
	MD015	University of Maryland/Greenebaum Cancer Center	4
	MD207	Maryland Proton Treatment Center	2
	MD157	UM Upper Chesapeake Medical Center	1
9	**LAPS-GA005**	**Emory University - Winship Cancer Institute LAPS**	**6**
	GA005	Emory University Hospital/Winship Cancer Institute	6
	LAPS-OH029	**CWRU Case Comprehensive Cancer Center LAPS**	**6**
	OH029	Case Western Reserve University	5
	OH248	UHHS-Westlake Medical Center	1
10	**GULFSOUTH**	**Gulf South Minority Underserved NCORP**	**5**
	LA034	Willis-Knighton Medical and Cancer Center	5
	MI005	**William Beaumont Hospital-Royal Oak**	**5**
	MI128	William Beaumont Hospital - Troy	2
	MI005	William Beaumont Hospital-Royal Oak	2
	MI015	Beaumont Hospital - Dearborn	1
11	**67029**	**Kantonsspital Aarau**	**2**
	67029	Kantonsspital Aarau	2
	FL020	**Orlando Health Cancer Institute**	**2**
	FL020	Orlando Health Cancer Institute	2
12	**LAPS-WA008**	**Fred Hutchinson Cancer Research Center LAPS**	**1**
	WA020	University of Washington Medical Center - Montlake	1

Secondary Objectives: Patient-Reported Outcome

- To compare the development of patient-reported outcome
  - Symptom burden [MDASI-Lung]),
  - Shortness Breath Questionnaire [SOBQ]
  - Health utility EuroQol [EQ5D]

PROs: Purpose/Hypothesis/Significance

Purpose: Investigate the patient-reported symptoms related to pulmonary toxicity (pneumonitis) and esophagitis between proton and proton CRT

Hypothesis: Compared with patients receiving either 3DCRT or IMRT (Arm 1), patients on the proton arm (Arm 2) will have less-severe "shortness of breath" and "sore throat" on MDASI-Lung 6 months after the end of concurrent chemoradiation therapy (representing late adverse response to radiation), and that the differences in symptom ratings between Arms will be clinically meaningful, after controlling for disease progression

Significance: PRO data will fill the gap of "disconnect" impression on toxicity-driven symptom burden or treatment benefit between arms, especially meaningful for interpreting each grade of toxicities

PRO/CER Measures, Assessment Intervals

Patients will be given the **4 instruments** in the clinic at **5 specified visits** at baseline, at week 6 (end of CRT), and at 3m (1st F/U visit), 6m, and 12ms after CRT:

- MD Anderson Symptom Inventory lung cancer module (MDASI-Lung), plus “difficulty swallowing” from MDASI-Item Library: 23 items, on 0-10 scale
- Shortness of Breath Questionnaire (SOBQ): 45 items, on 0-5 scale
- EQ-5D-5L: scale from 1-5
- Medical Service Use Survey

Perspectives on PRO Data Compliance

PRO Data Collection: by Dec 2020, 82% consented (41 vs. 185)

One site <70% consent on PROs (n=11); 1 site no Spanish speaking pts consent (n=6); 2 sites with only 1 enrolled w/o PROs (n=2); 2 sites with half consent on PROs (n=4); Other sites: consent >75%

Challenges:

1. Protocol page 77: “Patient participation in the QOL component is not mandatory in this study”
2. PRO tools in English only

Potential Solutions: NRG RTOG-1308 protocol amendment:

1. Remove wording of non “mandatory”
2. Adding Spanish, French, German versions of the tool

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PROs* may Become a Critical Outcome Measurement for this Trial - Collect Every PRO!

RTOG 1308 - MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC)

	Baseline[1]	6 Weeks Post ChemoRT Start[2]	4-8 Weeks Post ChemoRT End[2]	6 Months Post ChemoRT End[3]	12 Months Post ChemoRT End[4]
Forms expected	176	129	120	93	76
% completed of forms expected	141 (80.1%)	96 (74.4%)	86 (71.7%)	50 (53.8%)	42 (55.3%)
% with reason missing supplied by site	28 (15.9%)	33 (25.6%)	34 (28.3%)	42 (45.2%)	34 (44.7%)
Assessment completed too early	--	3 (9.1%)	7 (20.6%)	2 (4.8%)	3 (8.8%)
Assessment completed too late	15 (53.6%)	5 (15.2%)	--	11 (26.2%)	7 (20.6%)
Institutional error	2 (7.1%)	6 (18.2%)	5 (14.7%)	3 (7.1%)	2 (5.9%)
Other reason	7 (25.0%)	6 (18.2%)	7 (20.6%)	8 (19.0%)	11 (32.4%)
Patient refused due to illness	2 (7.1%)	8 (24.2%)	7 (20.6%)	10 (23.8%)	2 (5.9%)
Patient refused for other reason	--	3 (9.1%)	6 (17.6%)	7 (16.7%)	6 (17.6%)
Patient unable to be contacted	1 (3.6%)	2 (6.1%)	2 (5.9%)	1 (2.4%)	3 (8.8%)
Tool not available in patient's language	1 (3.6%)	--	--	--	--
% missing of forms expected	7 (4.0%)	--	--	1 (1.1%)	--

[1] On or before treatment start date
[2] +/- 7 days
[3] +/- 30 days
[4] +/- 45 days

*PROs: MDASI-LC, MDASI-swallow, EQ-5D-5L
Medical Service Use Survey, Shortness of Breath Questionnaire

Monthly Newsletter (Funding per Case)

NRG-RTOG 1308 Newsletter **July 2018**

Reminder:
Supplemental Site Funding!!!

See table summary below and see full Funding Sheet on the CTSU website.

In This Issue
- Amendment Update
- Education & Promotion
- Unique Protocol-Specific Requirements
- Enrollment
- Supplemental Site Funding

Funding Source and Study Component		Mandatory /Mandatory Request or Event/ Optional	NCTN Funding Amount per Patient Standard/ LAPS	NCORP Funding per Patient Standard/ LAPS
Federal	Base Intervention (Standard/ High Performance (HP) LAPS & NCORP)	Mandatory	$2250 / $4000	$4000
Federal	Biospecimen – H&E slides	Optional	$100	$100
Federal	Biospecimen – primary tumor block	Optional	$200	$200
Federal	Biospecimen – serum	Optional	$50	$50
Federal	Biospecimen – plasma	Optional	$100	$100
Federal	Biospecimen – whole blood	Optional	$50	$50
Federal	Quality of life	Optional	$1000	$1000
Total Potential Funds			**$3750 / $5500**	**$4000 / $5500**
Federal	Supplemental Site Funding	Mandatory	$2000	$2000
Total Potential Non-Federal Funds			**$2000**	**$2000**
Total Potential Funds			**$5750 / $7500**	**$6000 / $7500**

Phase IIIR Comparing Overall Survival After Photon vs. Proton ChemoRT

(Inoperable Stage II-IIIB NSCLC)

ACTIVATED	2/3/2014
Current accrual	283
Target accrual	330
Amendment 6 release date: Protocol Version Date:	12/13/2021 October 6, 2021
Total sites applied	105
Total sites approved	48

**** PSI – 1st patient treated at the first international site***

NOTE:
The trial is enrolling 3-4 patients/month. We hope to complete enrollment in another 12-16 months (47 more patients)!

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Challenges

- **Accrual, accrual, accrual!** - goal 5 patient/month, we need ALL participating centers to enroll one patient per month!

RTOG 1308:

A historical opportunity for our specialty!

Let's Do It!

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