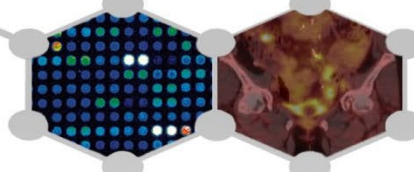

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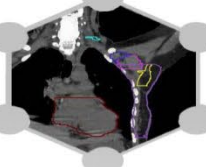

LU008 - Phase III Prospective Randomized Trial of Primary Lung Tumor Stereotactic Body Radiation Therapy Followed by Concurrent Mediastinal Chemoradiation for Locally-Advanced Non-Small Cell Lung Cancer

Charles B. Simone, II, MD

July 23, 2022

Disclosures

- National Institutes of Health
  - R01-CA255748-01A1
  - R42-CA-199735-02
  - HHSN272201800011C
- Varian Medical Systems grants, honorarium

Study Chairs

Principal Investigator: Charles B. Simone, II

Co-Principal Investigator: John Heinzerling

Radiation Oncology Chair: Jeffrey Bradley

Radiation Oncology Chair: Kristin Higgins

Medical Oncology Co-Chair: Kathryn Mileham

Translational Science Co-Chair: Mohamed Abazeed

Physics Co-Chair: Liyong Lin

PRO and NCORP Co-Chair: Nitin Ohri

Statistician: Chen Hu

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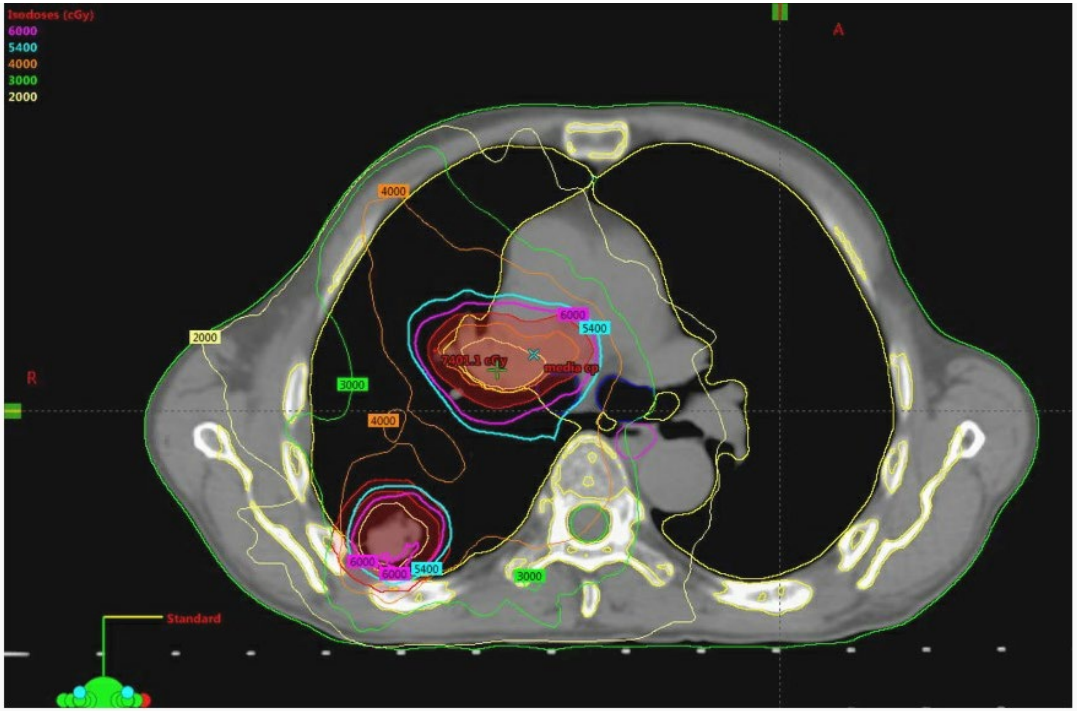
Hypotheses

- For LA-NSCLC, with concurrent chemoradiation followed by durvalumab, local control remains poor
  - Local failure drives new distant metastases and is highly predictive of cancer-related deaths
- As opposed to delivering SBRT as a boost, replacing conventionally fractionated radiotherapy with SBRT to the primary tumor followed by concurrent chemoradiation to the mediastinum will:
  - Be well-tolerated and associated with lower rates of radiation pneumonitis due to increase conformity with SBRT and less lung irradiate between the primary tumor and the mediastinum
  - Improve local control that will drive an improvement in progression-free survival and overall survival

Representative Case Example



Total volume of lung receiving 40 Gy= 332 cc (compared to 590 cc, 44% reduction)
Total volume of lung receiving 20 Gy=922 cc (compared to1300 cc, 29% reduction)
Total volume of lung receiving 10 Gy=2168 cc (compared to 2360, 8% reduction)

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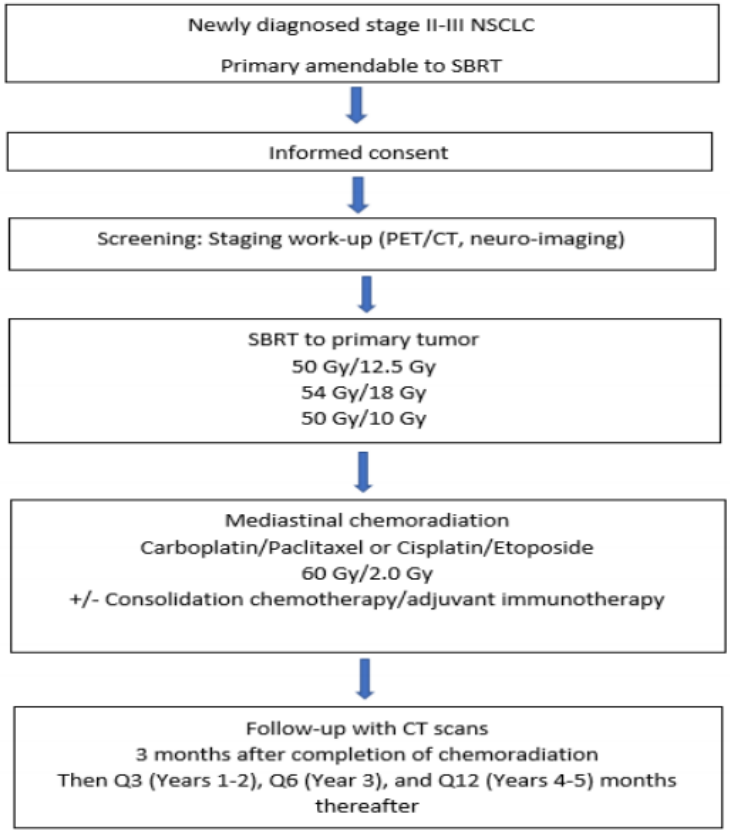
Ongoing Phase II Schema: Atrium Health/Levine Cancer Institute

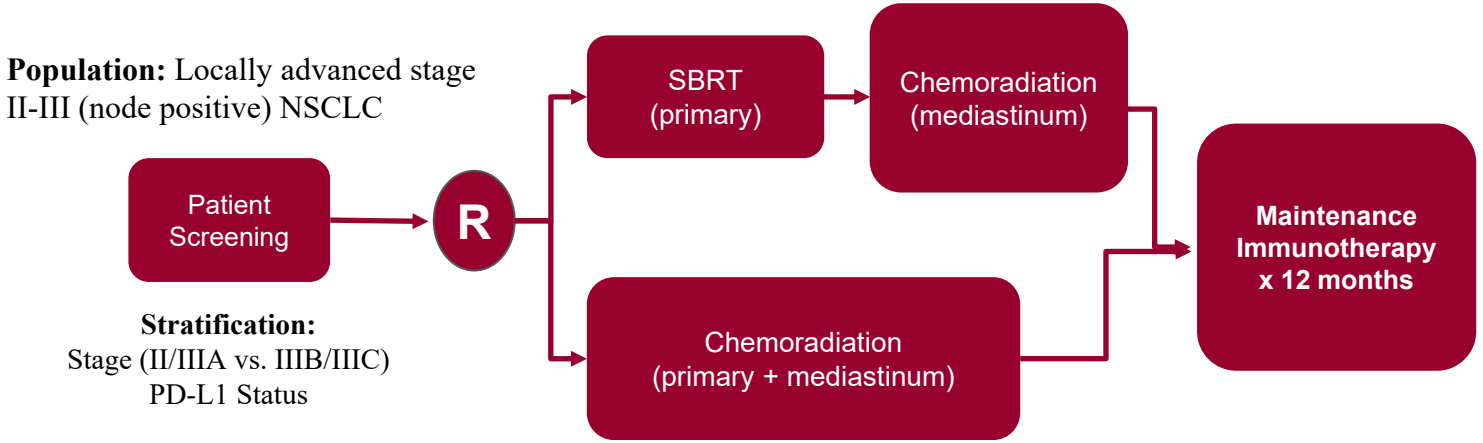


55 stage III NSCLC patients enrolled on a multi-site phase II single arm trial of SBRT to the primary followed by chemoradiation to the mediastinum/hilum

- 1-year PFS for the whole cohort: 62% [RTOG 0617 ~45% (41.2-49.2% on 4 arms)
- 1-year PFS in pts receiving durvalumab (n=26): 70.3% [PACIFIC durva arm 58%]
- Median OS: 40.8 months
- No local failures, 12 total failures (distant n=10, regional n=2)
- Grade 4-5 toxicities: none
- Grade 3 toxicities: 1 esophagitis, 2 pneumonitis
- No grade ≥3 cardiac events related to SBRT or fractionated radiation

Heinzerling J, Simone CB 2nd, et al. 2020 ASCO Annual Meeting and 2022 ASTRO Annual Meeting

LU008 Schema: Phase III



- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - SBRT to primary tumor:
    - 3 fractions to 54 Gy (BED_{10} of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED_{10} of 112.5 Gy) [peripheral]
    - 5 fractions to 50 Gy (BED_{10} of 100 Gy) [peripheral or central]
  - Radiation to involved hilar/mediastinal lymph nodes: 2 Gy x 30 fx to 60 Gy, IMRT or proton therapy
  - Concurrent chemotherapy: carboplatin + paclitaxel, cisplatin + etoposide, cisplatin + pemetrexed, or carboplatin + pemetrexed
  - Maintenance immunotherapy: durvalumab x 12 months [if durvalumab is NOT given, carbo/paclitaxel pts receive 2 cycles of consolidation]

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Key Inclusion/Exclusion Criteria

- Inclusion
  - Histologic or cytologic documentation of NSCLC
  - Stage II-III disease
    - Medically inoperable or refuse surgery
    - Identified primary tumor and at least one nodal metastasis
    - Up to 4 cycles of systemic therapy prior to registration allowed
  - Primary tumor ≤ 7 cm
  - Age ≥ 18 yrs
  - ECOG Performance Status 0-2
- Exclusion
  - Central primary tumor location (within 2 cm of the proximal bronchial tree) that is <2cm from involved nodal disease
    - Expected to exclude <15% of patients [7/62 (11%) in ongoing phase II trial]
  - Prior in-field RT determined by the treating MD to impede study treatment

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Objectives

- Primary Objective
  - Compare overall survival in patients with stage II-IIIC inoperable node-positive NSCLC after image guided, motion-managed conventional RT to the primary tumor and nodal metastases (Arm 1) or after image guided, motion-managed SBRT to the primary tumor followed by conventionally fractionated RT to nodal metastases (Arm 2) both given with concurrent platinum-based chemotherapy
  - Progression-free survival
- Secondary Objectives
  - Objective response rate (RECIST v 1.1)
  - Local control
  - Patterns of failure (primary, locoregional, or distant)
  - Changes in pulmonary function
  - Changes in quality of life and patient-reported outcomes (FACT-TOI, EQ-5D-5L, PRO-CTCAE)
  - Acute and late toxicity profiles (CTCAEv5)
  - Prognostic value of baseline physical activity level (using wearable devices) with respect to chemoRT completion, decline in quality-of-life following chemoRT, PFS, and OS
  - Clinical and dosimetric predictors of physical activity decline during chemoradiotherapy
- Exploratory Objectives
  - Collect biospecimens for future analyses.
  - Regional lung ventilation and dose thresholds of ventilating lung regions associated with pulmonary toxicities

Statistics

- Design: hybrid superiority-noninferiority design (Freidlin 2007) to demonstrate one of the following two co-primary aims (trial considered “positive” if either aim is satisfied):
  - Overall survival in Arm 2 is superior to Arm 1 OR
  - Overall survival in Arm 2 is non-inferior to Arm 1 AND PFS in Arm 2 is superior to Arm 1
- We will conclude SBRT should not replace standard of care if we cannot exclude the possibility that SBRT is inferior to standard of care
  - 90% power to declare non-inferiority of SBRT at a 1-sided significance level of 0.025 (HR 1.12)
- If non-inferiority of OS is demonstrated, we will determine if SBRT is superior in OS
  - 70% power to detect the superiority of SBRT at a 1-sided type 1 error of 0.025 (HR=0.76)
  - Expected improvement in 5-yr OS 38% to 48%
- After non-inferiority of OS is demonstrated, we will assess PFS (1-sided type 1 error of 0.025, HR 0.71)
  - Expected improvement in 2-yr PFS from 41% to 53% and in 4-yr PFS from 31% to 44%

Sample Size, Accrual, Central Review

- Sample Size: 450 eligible patients → final targeted accrual 474 subjects
- Interim analyses: three interim futility analyses based on PFS (n=2) and OS (n=1)
- Accrual: anticipated 6-month ramp-up and then 9.5 pts/month, enrollment over 4.7 years
- Pre-treatment reviews of the first 3 patients enrolled per treatment arm from each institution

Status and Timeline

- NRG Research Strategy Committee approved 3/11/2021
- TMSC and CTEP approved the concept 1/10/2022
- Full protocol submitted to CTEP June 2022
- Anticipated activation: approximately November 2022
  - RTOG 1308 and EA5181 will both be approaching accrual completion, no other large locally advanced NSCLC competing trials across the entire NTCN
  - Please active the trial when available in late 2022 or very early 2023!!

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