Lung Cancer Workshop

Charles B. Simone II, MD, FACRO
Radiation Oncology Co-Chair of NRG LU-006
Chief Medical Officer New York Proton Center
Professor, Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center

July 23, 2022
NRG-LU006
NCT04158141 – PI = Andreas Rimner, MD

Phase III Randomized Trial of
Pleurectomy/Decortication + Chemotherapy
+/- Adjuvant Hemithoracic Intensity-Modulated
Pleural Radiation Therapy (IMPRINT)
for Malignant Pleural Mesothelioma (MPM)
Disclosures

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

- Pleurectomy/Decortication (P/D) has become a common lung-sparing surgical approach for MPM.
- Chemotherapy (platinum/pemetrexed) may be delivered in the neoadjuvant or adjuvant setting.
- Adjuvant hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) was developed at Memorial Sloan Kettering Cancer Center and found to be safe in a multi-institutional phase II study, with promising survival outcomes.
- A Phase III randomized National Clinical Trials Network (NCTN) trial (NRG-LU006) was designed to evaluate the efficacy of this lung-sparing trimodality treatment approach for resectable MPM.
NRG-LU006: Phase III Randomized Trial on IMPRINT for MPM

NRG-LU006 Study Design

Eligibility:
• Stage I-III MPM
• Resectable by lung-sparing P/D
• Epithelioid or biphasic subtype
• Age ≥18 and ≤80 years
• KPS ≥80%
• FEV1 ≥40%, DLCO ≥40% predicted

Stratification:
• Cell type: Epithelioid vs biphasic
• Macroscopic complete resection: R0/R1 vs R2
• Chemotherapy vs chemo/immunotherapy

Permissible alternatives:
• Neoadjuvant chemo → P/D
• Neoadjuvant chemo/immunotherapy or ipilimumab/nivolumab
• Neoadjuvant therapy prior to enrollment
• Intensity-Modulated Proton Therapy

P/D (MCR) → Pemetrexed (500mg/m2) + Cisplatin (or carboplatin) (75mg/m2) q21 days x4 cycles

1:1 n=150

IMPRINT (50.4/60 Gy in 28 fractions)

No adjuvant IMPRINT
Objectives

Hypothesis:
Addition of adjuvant IMPRINT is associated with an overall survival benefit compared to surgery + chemotherapy alone.

Primary Objective:
Improvement in median OS from 12 months (null hypothesis) to 20 months (alternative hypothesis) (calculated from the time of randomization)

Secondary Objectives:
- Local Failure-Free, Distant Metastases-Free and Progression-Free Survival
- Toxicities per CTCAE v5.0
- QOL (QLQ-Q30 and LC13) (10-point change at 9 months)

Exploratory Objectives:
- To build a multiparametric prognostic imaging model to improve clinical staging and target delineation
- To identify genomic and immunologic predictive biomarkers of radiation sensitivity and potential future therapeutic targets
- Test RapidPlan model for optimized RT plan development (Mt. Sinai collaboration with Dr. Dumane/Rosenzweig)
- Center patient volume ≤10 vs >10 pleurectomy/decortications per year
Inclusion criteria
• Pathologically confirmed stage I-IIIA MPM (epithelioid or biphasic)
• Amenable to P/D as determined by a thoracic surgeon
• Age ≥18 years and ≤80 years
• Karnofsky performance status ≥80%
• FEV1 ≥40%, DLCO ≥40% predicted
• Adequate liver and renal function

Exclusion criteria
• Sarcomatoid histology
• Continuous oxygen use
• Third space fluid that cannot be controlled by drainage
• Serious unstable medical illness (e.g. concurrent active malignancy, active infection, or acute congestive heart failure)
• Prior thoracic radiation therapy
• Pregnancy or lactating
Surgeon Credentialing

- MCR = goal of surgical resection in every patient
- Resection definitions per IASLC/IMIG guidelines
- Documentation of diaphragmatic, pericardial and chest wall invasion for accurate T-staging
- Documentation of unresectable areas + clip placement
- No intraoperative adjunctive therapies, i.e. heated chemotherapy, photodynamic therapy
- Systematic nodal sampling
- Number of MPM surgeries in the past 2 years (must be >5/year)
- Number of grade 4-5 toxicities within 30 days postop in the past 2 years
Central Radiation Oncology Review

- Central review of each patient assigned to IMPRINT arm
  1) Review of target and OAR delineation
  2) Review of radiation treatment plan

- 48-hour turnaround
NRG-LU006: Phase III Randomized Trial on IMPRINT for MPM

Current Status

• Accrual: 8 patients (1 Alliance, 7 NRG credits)
• Applications for Site Registration: 75
• Sites approved: 20 (MDACC and Temple University pending)
• Monthly conference calls with participating sites (3rd Friday of the month, 11:00 a.m. EST), all participating sites are welcome

• Recordings on target delineation and treatment planning on CTSU website
• QuinTeT recommendations incorporated

• Presentation to the International Member Committee at this meeting to recruit additional international sites
Incorporated changes:

– Allow for neoadjuvant systemic therapy prior to enrollment
– Allow for neoadjuvant chemo/anti-PD-1/L1 therapy or ipilimumab/nivolumab
– Adjust window for randomization to 0-8 weeks prior to RT
– Language changes to the consent

Amendment #1&2 Approved on 4/13/2022
NRG-LU006: Phase III Randomized Trial on IMPRINT for MPM

## Acknowledgments

### NRG-LU006 Study Investigators

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Institution/Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreas Rimner, MD</td>
<td>Memorial Sloan Kettering Cancer Center</td>
</tr>
<tr>
<td>Charles B. Simone, II, MD</td>
<td>New York Proton Center Rad. Oncology</td>
</tr>
<tr>
<td>Valerie W. Rusch, MD</td>
<td>Memorial Sloan Kettering Cancer Center Surg. Oncology</td>
</tr>
<tr>
<td>Marjorie G. Zauderer, MD</td>
<td>Memorial Sloan Kettering Cancer Center Med. Oncology</td>
</tr>
<tr>
<td>Ritu R. Gill, MD</td>
<td>Beth Israel Deaconess Medical Center Radiology</td>
</tr>
<tr>
<td>Ellen Yorke, PhD</td>
<td>Memorial Sloan Kettering Cancer Center Med. Physics</td>
</tr>
<tr>
<td>Zuofeng Li, DSc</td>
<td>University of Florida College of Medicine Proton Physics</td>
</tr>
<tr>
<td>Khinh Ranh Voong, MD MPH</td>
<td>Sidney Kimmel Cancer Center Statistics</td>
</tr>
<tr>
<td>Tobias Peikert, MD</td>
<td>Mayo Clinic Cancer Center Translational</td>
</tr>
<tr>
<td>Ming S. Tao, MD</td>
<td>Princess Margaret Cancer Center Pathology</td>
</tr>
<tr>
<td>Chen Hu, PhD</td>
<td>NRG Oncology Statistical and Data Management Center &amp; John Hopkins University School of Medicine Statistics</td>
</tr>
</tbody>
</table>

### Champions

<table>
<thead>
<tr>
<th>Champion</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Varlotto, MD</td>
<td>ECOG-ACRIN</td>
</tr>
<tr>
<td>Jeremy Brownstein, MD</td>
<td>Alliance</td>
</tr>
<tr>
<td>Robert Samstein, MD, PhD</td>
<td>SWOG</td>
</tr>
</tbody>
</table>
# Acknowledgments

NRG Operations and SDMC Team

<table>
<thead>
<tr>
<th>For Contact Information see protocol cover page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data Management</strong></td>
</tr>
<tr>
<td>Sylvia Solakov</td>
</tr>
<tr>
<td>Jeff Serianni</td>
</tr>
<tr>
<td><strong>RTQA</strong></td>
</tr>
<tr>
<td>Jennifer Presley</td>
</tr>
<tr>
<td><strong>Protocol Development</strong></td>
</tr>
<tr>
<td>Fran Bradley</td>
</tr>
<tr>
<td><strong>Lung Committee Chair</strong></td>
</tr>
<tr>
<td>Jeffrey D. Bradley</td>
</tr>
<tr>
<td><strong>Biostatistics</strong></td>
</tr>
<tr>
<td>Chen Hu, Rebecca Paulus</td>
</tr>
</tbody>
</table>

- This project is supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA180803 (IROC) from the National Cancer Institute (NCI)
- Patients
Contact

• Andreas Rimner (rimnera@mskcc.org)
• Fran Bradley