Primary endpoint analysis of a randomized phase III Trial of hypofractionated versus conventional post-prostatectomy radiotherapy: NRG Oncology GU003
Presented by Mark K. Buyyounouski, MD, Stanford University

Validation of a 22-gene genomic classifier in the NRG Oncology/RTOG 9202, 9413 and 9902 phase III randomized trials: A biopsy-based individual patient meta-analysis in high-risk prostate cancer
Presented by Paul L. Nguyen, MD, Dana-Farber/Brigham and Women's Cancer Center

Consolidative use of radiotherapy to block (CURB) oligoprogression: Interim analysis of the first randomized study of stereotactic body radiotherapy in patients with oligoprogressive metastatic cancers of the lung and breast
Presented by C. Jillian Tsai, MD, PhD, Memorial Sloan Kettering Cancer Center

Moderator: Andrea K. Ng, MD, MPH, FASTRO, Dana-Farber/Brigham and Women's Hospital

Featured Experts: Sophia C. Kamran, MD, Mass General Cancer Center
Steven J. Chmura, MD, PhD, University of Chicago
Primary Endpoint Analysis of a Randomized Phase III Trial of Hypofractionated versus Conventional Post-Prostatectomy Radiotherapy: NRG Oncology GU-003

Mark K. Buuyounouski, MD

Stanford University
Disclosures

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• **ClinicalTrials.gov Identifier:** NCT03274687

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Introduction

• **Postprostatectomy radiotherapy** is a well-established, albeit underutilized,$^{1,2}$ practice standard for biochemical recurrence (PSA-only) post-prostatectomy.$^3$

• **Hypofractionation** is a well-accepted practice standard for intact prostate cancer,$^4$ which may also be acceptable post-prostatectomy.

• **Quality-of-life** may be influenced by hypofractionation and is an determinant of acceptable practice standards.

2. Sineshaw et al, Eur Urol 2015  
3. Thompson et al, J Urol 2013  
4. Morgan et al, PRO 2018
## Benefits of Hypofractionation

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Benefit of fewer treatment days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Shorter time commitment</td>
</tr>
<tr>
<td></td>
<td>Greater access to a potentially curative treatment</td>
</tr>
<tr>
<td></td>
<td>Less expense related to travel and copays</td>
</tr>
<tr>
<td></td>
<td>Fewer absences from work and other responsibilities</td>
</tr>
<tr>
<td>Providers</td>
<td>Improved productivity of equipment and staff</td>
</tr>
<tr>
<td></td>
<td>Improved capacity for all patients</td>
</tr>
<tr>
<td>Payors</td>
<td>Lower cost</td>
</tr>
</tbody>
</table>
**Objective**

To determine if hypofractionated postprostatectomy radiotherapy (HYPORT) is non-inferior to conventionally fractionated postprostatectomy radiotherapy (COPORT) for patient-reported GI and GU symptoms.
NRG-GU003 Schema

Eligibility
1. PSA < 0.1ng/mL
   pT3 pN0/X
   or
   pT2 pN0/X & +Margin

2. PSA ≥ 0.1ng/mL
   pT2/3pN0/X

Stratification
1. Baseline EPIC score (four tier based on GI and GU scores)
2. ADT ≤ 6 months (yes vs. no)

Note: Lymph node RT was not allowed

COPORT
Prostate Bed RT
1.8 Gy X 37 = 66.6 Gy

HYPORT
Prostate Bed RT
2.5 Gy X 25 = 62.5 Gy
Mean EPIC GU Domain Scores

$p = 0.70 \quad p = 0.77 \quad p = 0.37 \quad p = 0.78 \quad p = 0.81$
## GU Change Scores

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>COPORT</th>
<th>HYPORT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of RT Score</td>
<td>(n = 133)</td>
<td>(n = 112)</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-4.3 ± 22.6</td>
<td>-7.9 ± 20.9</td>
<td></td>
</tr>
<tr>
<td>6 Month Score</td>
<td>(n = 110)</td>
<td>(n = 119)</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>0.1 ± 20.3</td>
<td>-1.7 ± 18.6</td>
<td></td>
</tr>
<tr>
<td>12 Month Score</td>
<td>(n = 116)</td>
<td>(n = 116)</td>
<td>0.66</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-2.3 ± 22.6</td>
<td>-5.4 ± 21.2</td>
<td></td>
</tr>
<tr>
<td>24 Month Score*</td>
<td>(n = 117)</td>
<td>(n = 100)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-3.0 ± 23.3</td>
<td>-5.2 ± 22.8</td>
<td></td>
</tr>
</tbody>
</table>

*Co-Primary Endpoint
Mean EPIC GI Domain Scores

- Baseline: $\text{p} = 0.41$
- End of RT: $\text{p} < 0.001$
- 6 Month: $\text{p} = 0.58$
- 12 Month: $\text{p} = 0.92$
- 24 Month: $\text{p} = 0.50$

---

**Legend:**
- **COPORT**
- **HYPORT**
# GI Change Scores

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>COPORT</th>
<th>HYPORT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of RT Score</td>
<td>(n = 133)</td>
<td>(n = 112)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-6.8 ± 15.8</td>
<td>-15.0 ± 21.3</td>
<td></td>
</tr>
<tr>
<td>6 Month Score</td>
<td>(n = 110)</td>
<td>(n = 119)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-1.9 ± 13.6</td>
<td>-2.7 ± 14.0</td>
<td></td>
</tr>
<tr>
<td>12 Month Score</td>
<td>(n = 116)</td>
<td>(n = 116)</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-2.7 ± 12.7</td>
<td>-3.1 ± 13.9</td>
<td></td>
</tr>
<tr>
<td>24 Month Score*</td>
<td>(n = 117)</td>
<td>(n = 100)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean ± Std. Dev.</td>
<td>-1.5 ± 14.1</td>
<td>-2.2 ± 13.2</td>
<td></td>
</tr>
</tbody>
</table>

*Co-Primary Endpoint
Conclusions

**NRG-GU003**

- HYPORT is associated with greater patient-reported GI toxicity compared to COPORT at the completion of RT.
- HYPORT is non-inferior to COPORT in terms of patient-reported GU or GI toxicity at 2 years.
- HYPORT is a new acceptable practice standard for patients receiving postprostatectomy radiotherapy.
Validation of a 22-Gene Genomic Classifier in the NRG Oncology/RTOG 9202, 9413 and 9902 Phase III Randomized Trials: A Biopsy-Based Individual Patient Meta-Analysis in High-Risk Prostate Cancer

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Harvard Medical School
Disclosure

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Background

• High Risk Prostate Cancer accounts for 2/3 of the deaths from localized prostate cancer

• Current radiation is a “one-size fits all” scheme of RT+long-term ADT

• The use of genomic testing to stratify patients into cohorts with higher and lower risk of metastases could allow for personalization of therapy
Method

• We validated the performance of the Decipher 22-Gene Genomic Classifier (GC) in pre-treatment biopsy samples collected in three randomized phase III high-risk definitive radiotherapy trials: NRG/RTOG 92-02, 94-13, and 99-02.

• These tissue samples were collected up to 29 years ago.
RESULTS: GC Was Prognostic for DM, PCSM, OS on UVA

- **DM**:
  - RTOG 9202: HR [1.12; 1.50], P-value <0.001*, Weight 44.7%
  - RTOG 9413: HR [1.07; 1.45], P-value <0.001*, Weight 40.8%
  - RTOG 9902: HR [1.12; 1.86], P-value <0.001*, Weight 14.5%
  - **Overall effect**: HR [1.18; 1.43], Weight --

- **PCSM**:
  - RTOG 9202: HR [1.10; 1.57], P-value 0.002*, Weight 33.7%
  - RTOG 9413: HR [1.10; 1.43], P-value 0.002*, Weight 59.5%
  - RTOG 9902: HR [1.07; 2.35], P-value 0.002*, Weight 6.8%
  - **Overall effect**: HR [1.17; 1.43], Weight --

- **OS**:
  - RTOG 9202: HR [1.05; 1.30], P-value 0.004*, Weight 35.4%
  - RTOG 9413: HR [1.04; 1.24], P-value 0.004*, Weight 50.4%
  - RTOG 9902: HR [0.97; 1.35], P-value 0.004*, Weight 14.2%
  - **Overall effect**: HR [1.08; 1.22], Weight --

Heterogeneity: $I^2 = 0\%$, $p = 0.62$ for DM.

Heterogeneity: $I^2 = 0\%$, $p = 0.52$ for PCSM.

Heterogeneity: $I^2 = 0\%$, $p = 0.93$ for OS.
RESULTS: On MVA, GC Was Still Prognostic for DM, PCSM, OS

<table>
<thead>
<tr>
<th>Variable</th>
<th>DM</th>
<th>PCSM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC score</td>
<td>1.24 (1.11 - 1.39)</td>
<td>&lt;0.001*</td>
<td>1.27 (1.13 - 1.43)</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.98 - 1.06)</td>
<td>0.42</td>
<td>1.04 (0.99 - 1.09)</td>
</tr>
<tr>
<td>Log2 PSA</td>
<td>0.98 (0.79 - 1.22)</td>
<td>0.87</td>
<td>0.96 (0.77 - 1.19)</td>
</tr>
<tr>
<td>T3-T4 vs. T1-T2</td>
<td>1.50 (0.87 - 2.60)</td>
<td>0.14</td>
<td>1.43 (0.80 - 2.56)</td>
</tr>
<tr>
<td>Gleason 8-10 vs. &lt;8</td>
<td>2.52 (1.42 - 4.46)</td>
<td>0.002*</td>
<td>1.56 (0.87 - 2.78)</td>
</tr>
</tbody>
</table>

Hazard ratios of genomic classifiers were per 0.1 unit increased. Strata = original arm.
Conclusions

• This is the first validation of any gene expression biomarker on pre-treatment biopsy samples from prospective randomized trials and demonstrates an independent association of GC score with DM, PCSM, and OS.

• High-risk prostate cancer is a heterogeneous disease state and GC can improve risk stratification to help personalize shared decision-making.

• NRG-GU009/Predict-RT (NCT04513717) will further determine the optimal therapy based on GC score.
Expert Perspective

Sophia C. Kamran, MD
Mass General Cancer Center
Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression: Interim Analysis of the First Randomized Study of Stereotactic Body Radiotherapy in Patients with Oligoprogressive Metastatic Cancers of the Lung and Breast

C. Jillian Tsai, MD, PhD

Memorial Sloan Kettering Cancer Center
Disclosure

• Employer: Memorial Sloan Kettering Cancer Center
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  • Memorial Sloan Kettering Cancer Department of Radiation Oncology Research Funds
  • Varian Medical Inc.

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¹Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, ²Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, ³Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, ⁴Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY
• **Second-line systemic therapy**
  
  - **Non-small-cell lung cancer (NSCLC)**
    - PDL-1 positive; Pembrolizumab; PFS = 4 months (Lancet 2016)
    - After platinum: Ramucirumab + Docetaxel; PFS = 4.5 months (Lancet 2014)
    - After first-line EGFR-TKI: Osimertinib; PFS = 10.1 months (NEJM 2017)
    - After Osimertinib: No standard
  
  - **Breast**
    - ER+ after first-line ET: Fulvestrant + CDK4/6 inhibitor; PFS = 9.5-20.5 months
    - TNBC after first-line: No standard; PFS = 2.3-5.6 months
Method

• **Primary objective:**
  - Progression-free survival

• **Accrual goal:**
  - 160 (80 each arm)
  - Current accrual: 106/160

• **Study timeline:**
  - Serial follow up imaging up to 52 weeks
Results – Progression-Free Survival (Entire Cohort)

- **SBRT**: Median PFS: 31 weeks
- **No SBRT**: Median PFS: 11 weeks

Log-rank p=0.002

Number at risk
- SBRT: 55, 39, 30, 25, 18, 10
- No SBRT: 51, 25, 11, 7, 6, 4

Median follow up: 45 weeks; 58 weeks for living patients.

78 of 106 patients further progressed.

39 of 106 (37%) died.
Results – PFS by Primary Disease Sites

**Lung (40 of 59 progressed)**

- **SBRT**
  - Median PFS: 44 weeks
- **No SBRT**
  - Median PFS: 9 weeks

Log-rank p=0.001

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBRT</td>
<td>31</td>
<td>24</td>
<td>22</td>
<td>19</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>No SBRT</td>
<td>28</td>
<td>12</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Breast (38 of 47 progressed)**

- **SBRT**
  - Median PFS: 18 weeks
- **No SBRT**
  - Median PFS: 19 weeks

Log-rank p=0.478

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBRT</td>
<td>24</td>
<td>15</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>No SBRT</td>
<td>23</td>
<td>13</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
### Results – Adverse Events and Sites of Further Progression

#### Toxicities

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>No SBRT (N=51)</th>
<th>SBRT (N=55)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event, grade ≥ 2</td>
<td>15 (40%)</td>
<td>23 (61%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pneumonitis, grade 2</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Diarrhea, grade 2</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Gastrointestinal reflux, grade 2</td>
<td>0</td>
<td>1 (1.8%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Dyspnea, grade 3</td>
<td>1 (2.0%)</td>
<td>0</td>
<td>0.48</td>
</tr>
</tbody>
</table>

#### New Lesions

<table>
<thead>
<tr>
<th>New Lesions</th>
<th>Lung (N=40)</th>
<th>Breast (N=38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>18 (45.0%)</td>
<td>34 (89.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>18 (45.0%)</td>
<td>3 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (10.0%)</td>
<td>1 (2.6%)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• In this pre-planned interim analysis, we demonstrated the benefit of SBRT to sites of oligoprogression on overall PFS, meeting the primary endpoint.
  • The difference was driven by the substantial response in NSCLC cohort.
    • Median PFS = 44 weeks, longer than many further lines of systemic therapy.
  • No benefit of SBRT seen in the breast cohort.
    • Most breast patients developed new lesions upon further progression.

• SBRT to oligoprogression had acceptable toxicity profiles.

• The mechanism of the differential benefits between NSCLC and breast cohorts merits further evaluation.
Expert Perspective

Steven J. Chmura, MD, PhD

University of Chicago
Question & Answer

Please submit your questions in the chat.
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