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NEWS BRIEFING #1

October 25, 2021

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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. Buyyounouski, MD

Stanford University

Disclosures

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- **ClinicalTrials.gov Identifier**: NCT03274687
- Full author list:

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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.

1. Mahal et al, Clin Genitourin Cancer 2015
2. Sineshaw et al, Eur Urol 2015
3. Thompson et al, J Urol 2013
4. Morgan et al, PRO 2018

Benefits of Hypofractionation

Stakeholder	Benefit of fewer treatment days
Patients	Shorter time commitment Greater access to a potentially curative treatment Less expense related to travel and copays Fewer absences from work and other responsibilities
Providers	Improved productivity of equipment and staff Improved capacity for all patients
Payors	Lower cost

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

RANDOMIZE

1:1

COPORT
Prostate Bed RT
1.8 Gy X 37 = 66.6 Gy

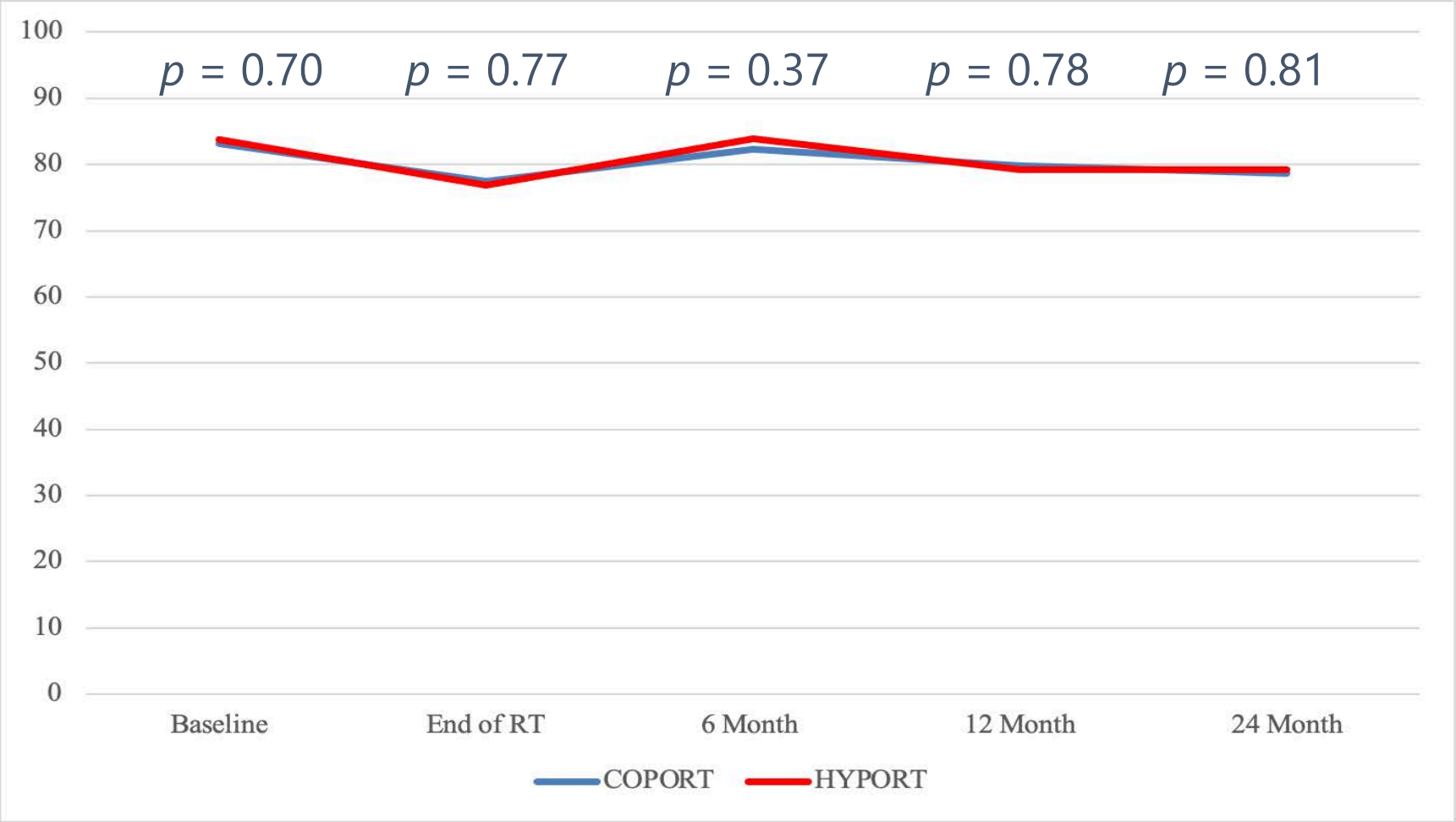
HYPORT
Prostate Bed RT
2.5 Gy X 25 = 62.5 Gy

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

Mean EPIC GU Domain Scores

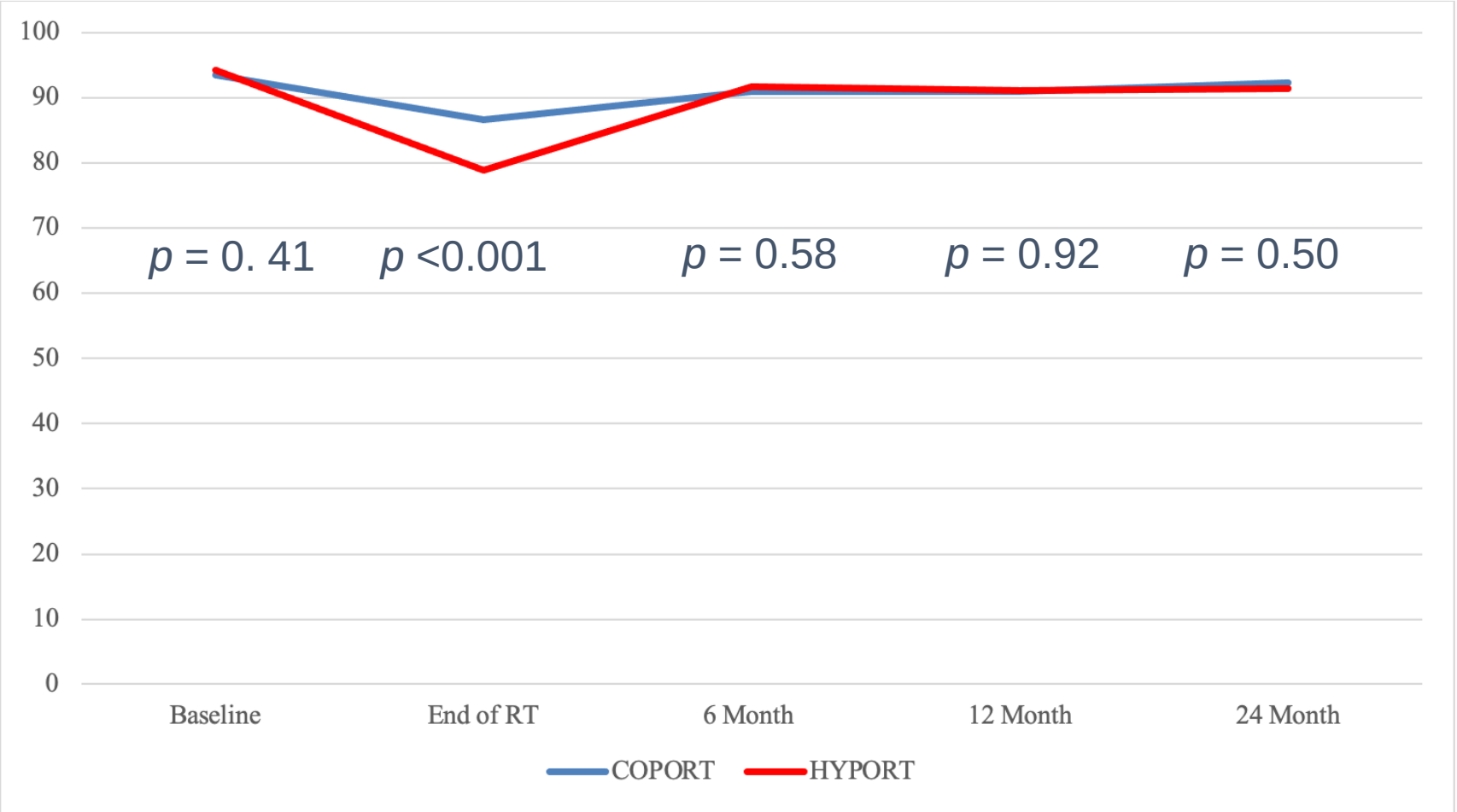


GU Change Scores

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

***Co-Primary Endpoint**

Mean EPIC GI Domain Scores



GI Change Scores

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

***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.

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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

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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

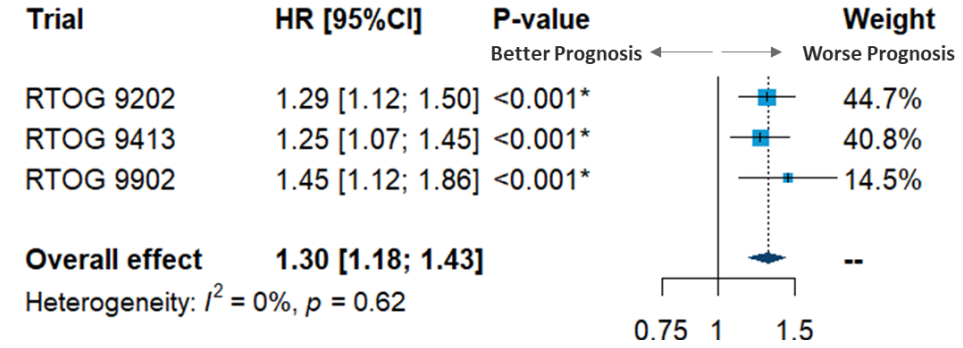
Method

- 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.

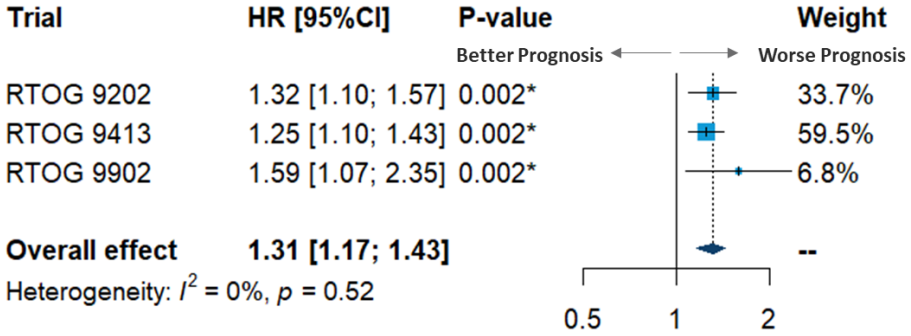
RESULTS: GC Was Prognostic for DM, PCSM, OS on UVA

DM



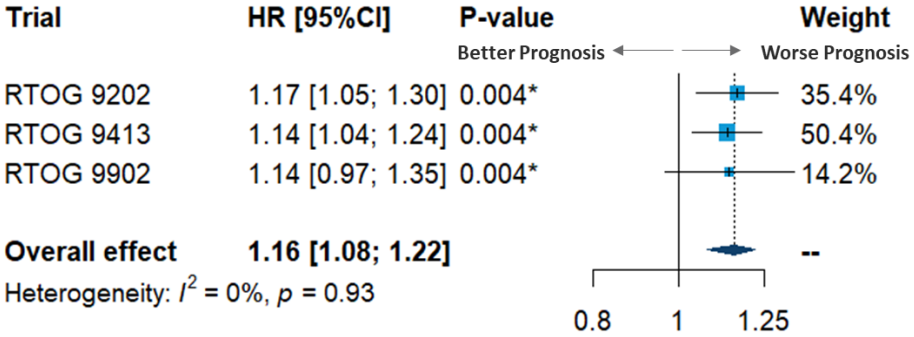
Distant Metastasis

PCSM



PCSM

OS



OS

RESULTS: On MVA, GC Was Still Prognostic for DM, PCSM, OS

Variable	DM		PCSM		OS	
	Hazard Ratio (95% CI), P-value					
GC score	1.24 (1.11 - 1.39)	<0.001*	1.27 (1.13 - 1.43)	<0.001*	1.12 (1.05 - 1.20)	0.001*
Age	1.02 (0.98 - 1.06)	0.42	1.04 (0.99 - 1.09)	0.15	1.07 (1.04 - 1.10)	<0.001*
Log2 PSA	0.98 (0.79 - 1.22)	0.87	0.96 (0.77 - 1.19)	0.70	1.01 (0.88 - 1.15)	0.90
T3-T4 vs. T1-T2	1.50 (0.87 - 2.60)	0.14	1.43 (0.80 - 2.56)	0.23	1.19 (0.85 - 1.67)	0.30
Gleason 8-10 vs. <8	2.52 (1.42 - 4.46)	0.002*	1.56 (0.87 - 2.78)	0.13	1.40 (0.99 - 1.99)	0.06

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

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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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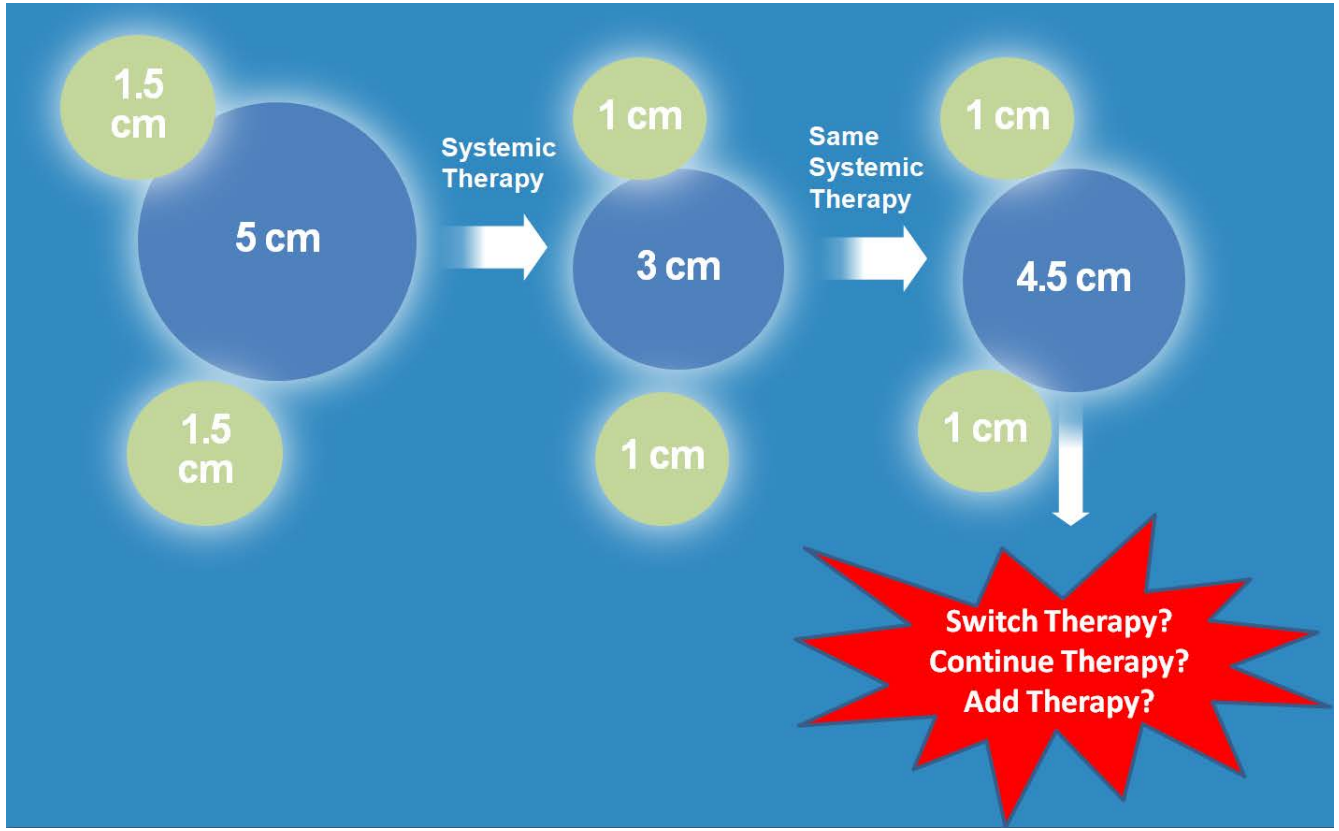
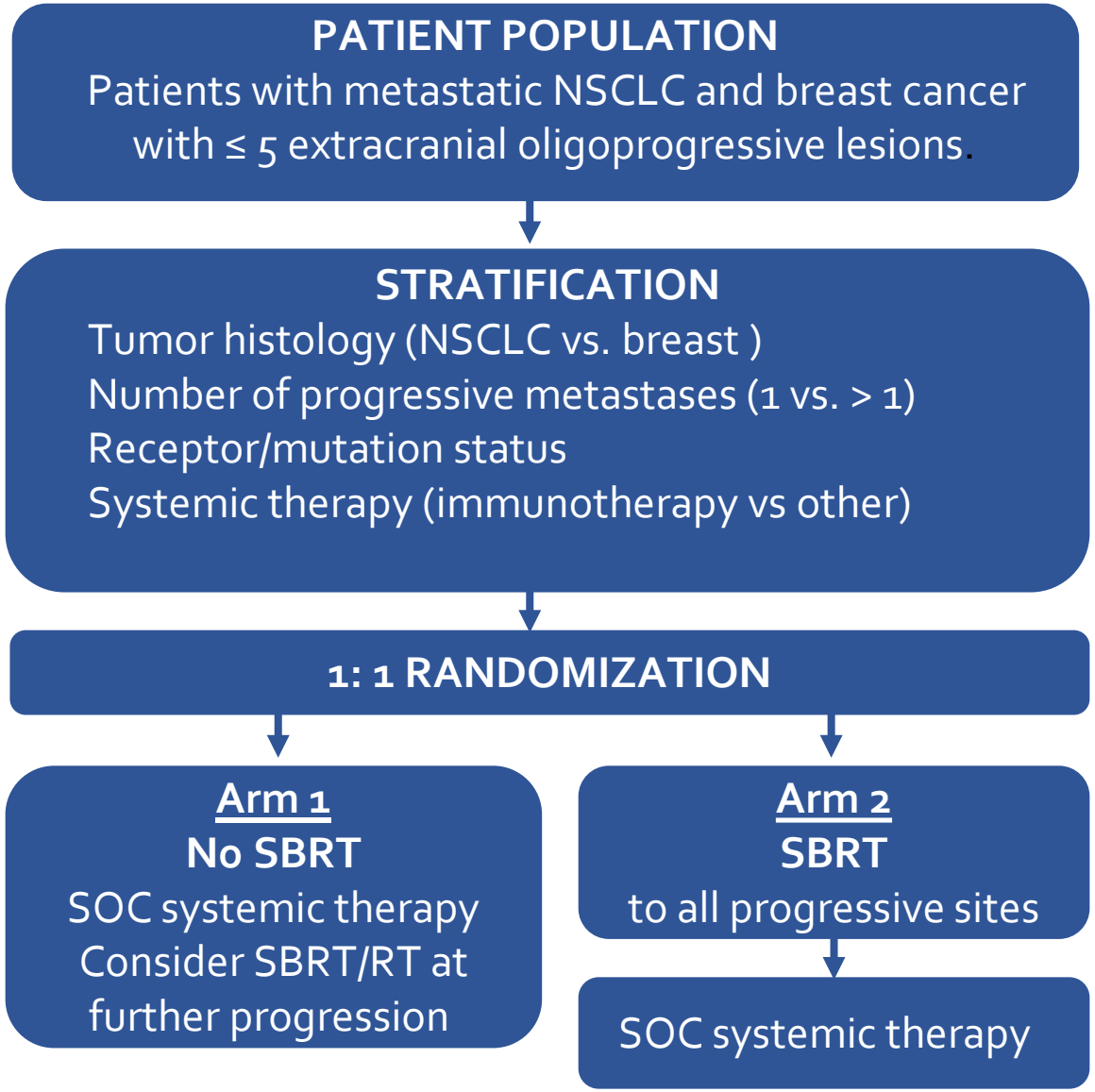
Background



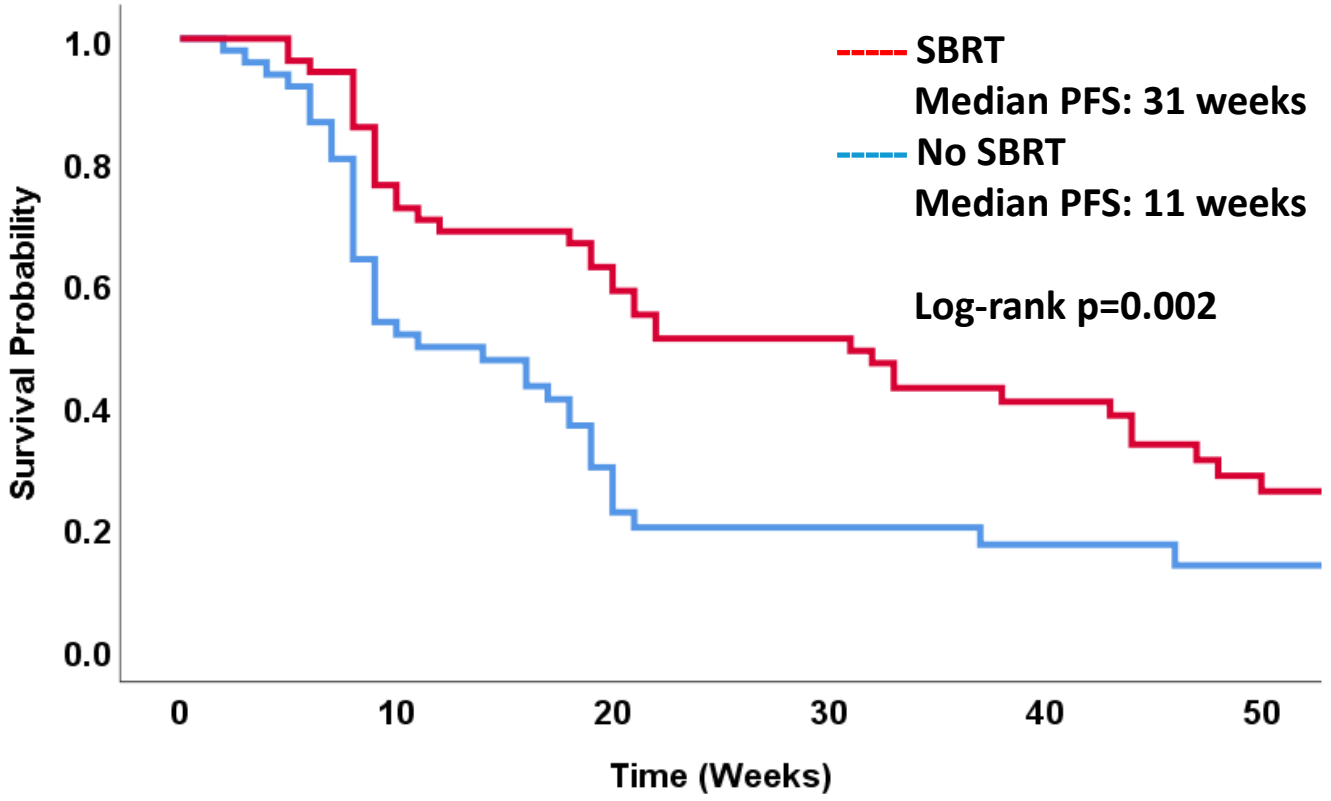
- **Second-line systemic therapy**
  - Non-small-cell lung cancer (NSCLC)
    - PDL-1 positive; Pembrolizumab; PFS= 4 months (Lancet 2016)
    - After platinum: Ramucirumab + Docetaxel; PFS = 4.5 months (Lancet 2014)
    - After first-line EGFR-TKI: Osimertinib; PFS = 10.1 months (NEJM 2017)
    - After 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)



Number at risk

SBRT	55	39	30	25	18	10
No SBRT	51	25	11	7	6	4

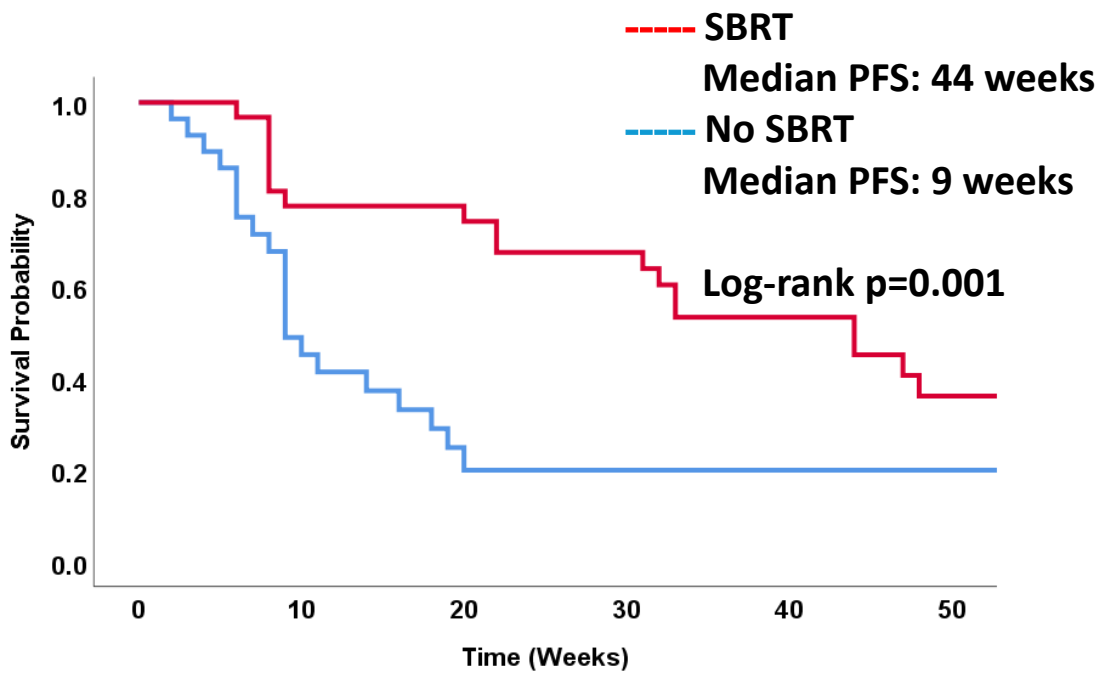
Median follow up: 45 weeks; 58 weeks for living patients.

78 of 106 patients further progressed.

39 of 106 (37%) died.

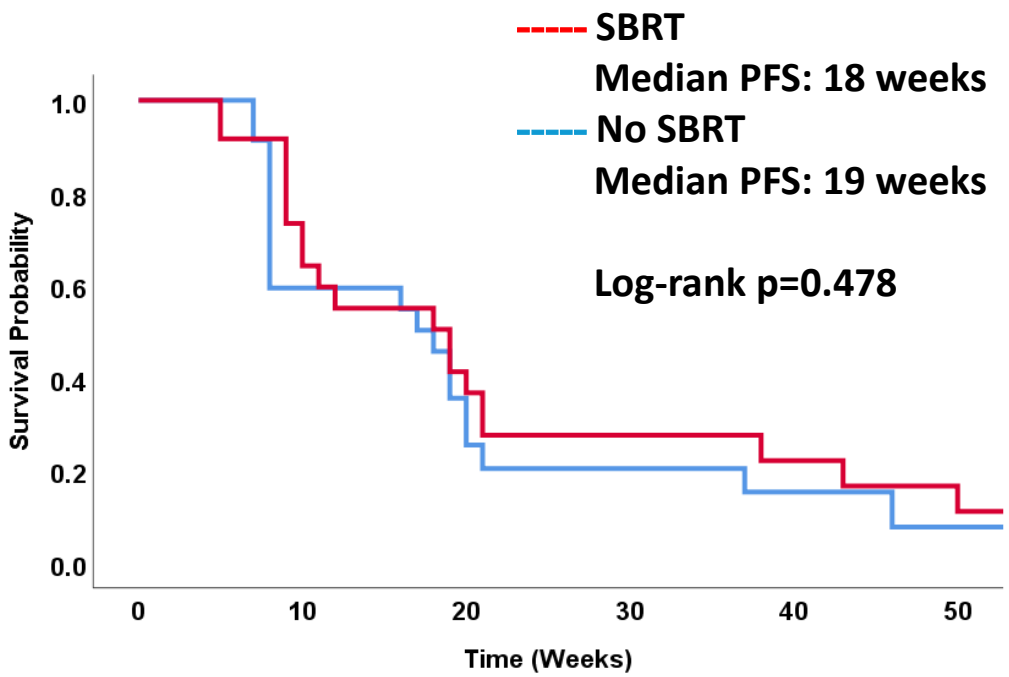
Results – PFS by Primary Disease Sites

Lung (40 of 59 progressed)



Number at risk						
SBRT	31	24	22	19	14	8
No SBRT	28	12	4	3	3	3

Breast (38 of 47 progressed)



Number at risk						
SBRT	24	15	8	6	4	2
No SBRT	23	13	6	4	3	1

Results – Adverse Events and Sites of Further Progression

Toxicities	No SBRT (N=51)	SBRT (N=55)	p
Any adverse event, grade ≥ 2	15 (40%)	23 (61%)	0.13
Pneumonitis, grade 2	0	1 (1.8%)	0.52
Diarrhea, grade 2	0	1 (1.8%)	0.52
Gastrointestinal reflux, grade 2	0	1 (1.8%)	0.52
Dyspnea, grade 3	1 (2.0%)	0	0.48

New Lesions	Lung (N=40)	Breast (N=38)	p
Yes	18 (45.0%)	34 (89.5)	<0.001
No	18 (45.0%)	3 (7.9%)	
Unknown	4 (10.0%)	1 (2.6%)	

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

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Question & Answer

Please submit your questions in the chat.

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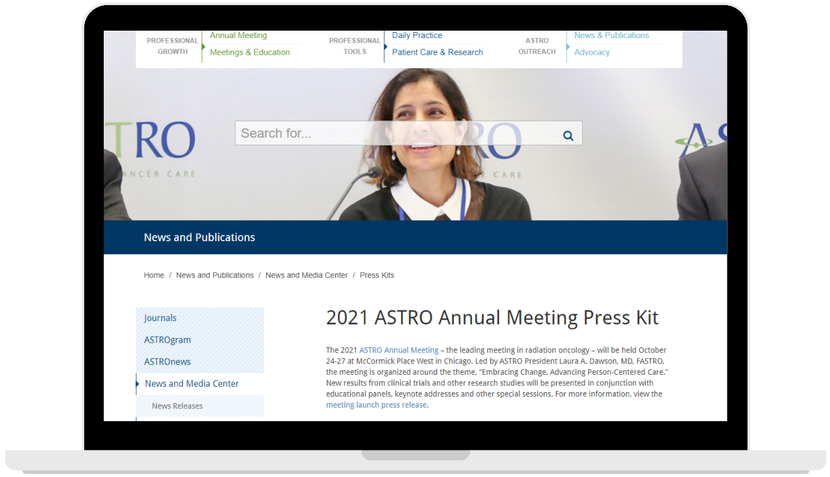

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