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No Role for Stereotactic Body Radiation Therapy in Oligometastatic Breast Cancer

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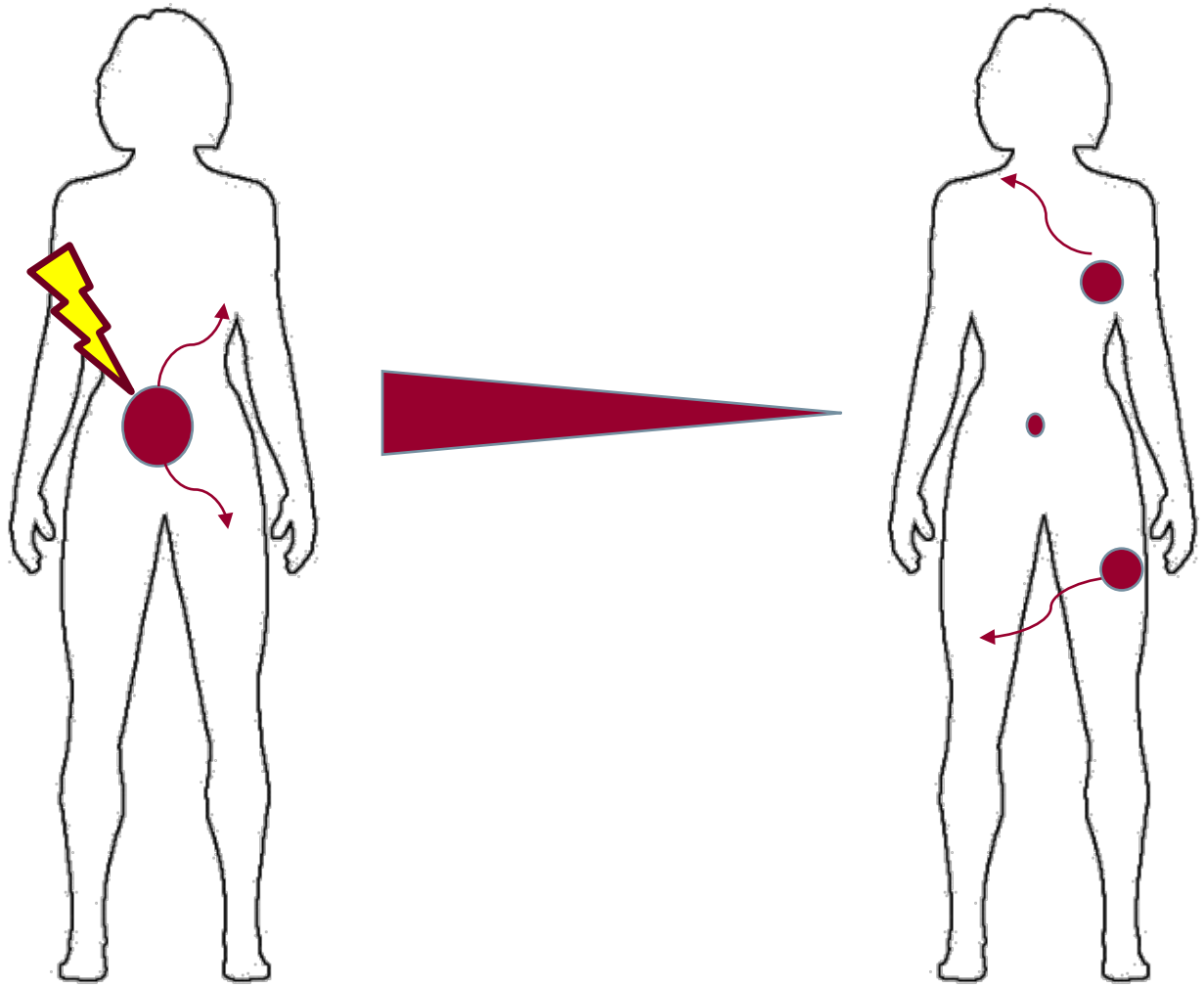
Radiotherapy (XRT) Palliates Symptoms in Patients with Metastatic Breast Cancer



Initial metastasis

Progression of Known/New Mets

Traditional XRT Role:
XRT leads to regression of treated metastasis with **no impact** on progression or development of new metastases outside of the XRT field

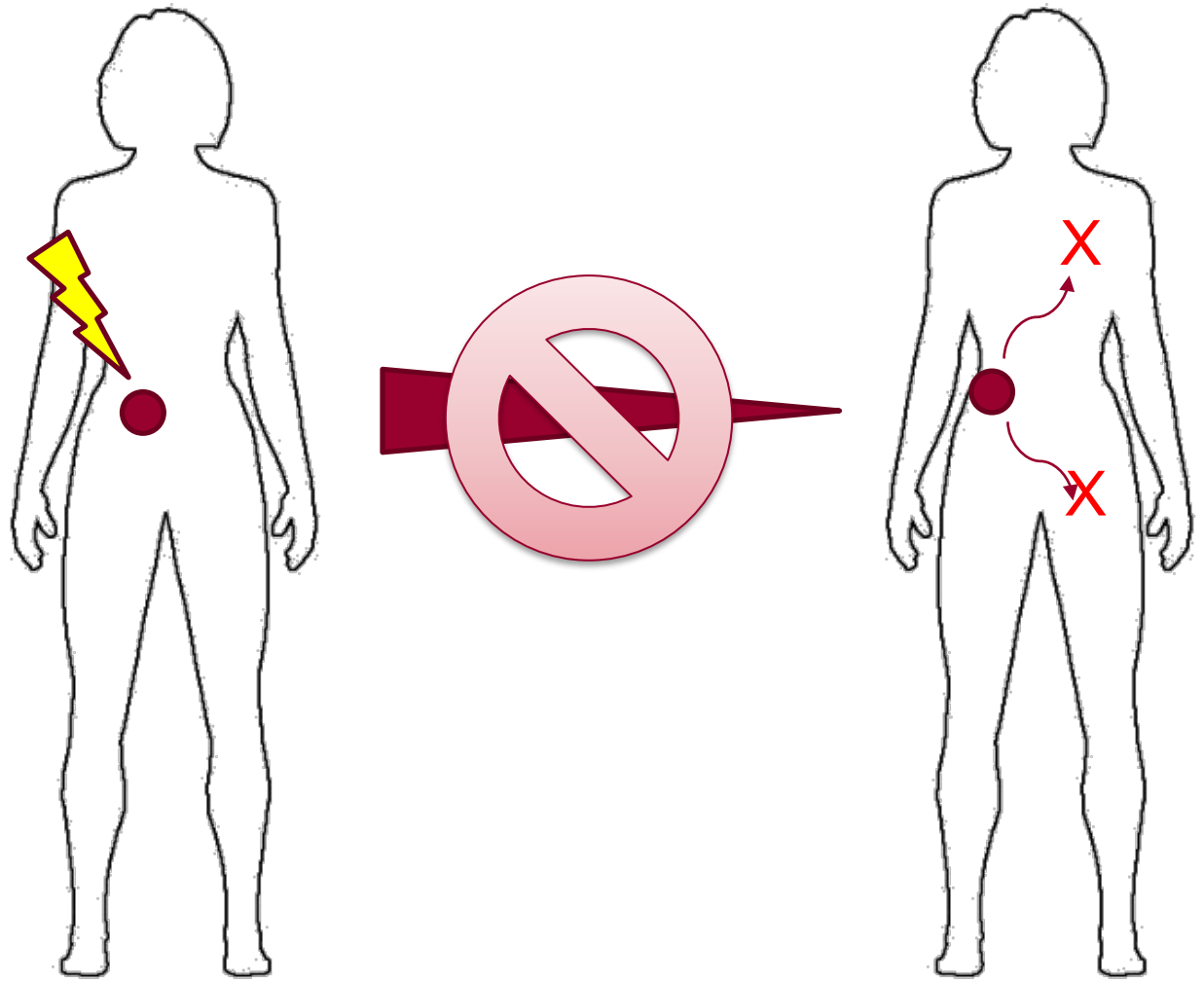
Favorable Prognostic Factors in Patients with Metastatic Breast Cancer

- Smaller number of metastatic lesions (4 or less) is better than larger number of metastases
- Longer time interval from definitive treatment to development of first metastases is better than metastatic disease that arises within a short interval
- Hormone receptor positive breast cancer that has spread to the bone only is more favorable than disease that has spread to the viscera (e.g., liver, lungs, brain) although there are exceptions

Hypothesis

Stereotactic body radiation (SBRT) will benefit patients with oligometastasis within the bone not viscera that arise after a prolonged period of time in patients with hormone receptor positive, Her2 negative breast cancer

Prevent progression of current and new metastases



Initial metastases

Progression of Known/New

Ablative therapies (surgery or high dose focused radiation on mets) – may improve PFS and OS in patients with oligomets by preventing progression of known metastases and development of new lesions elsewhere.

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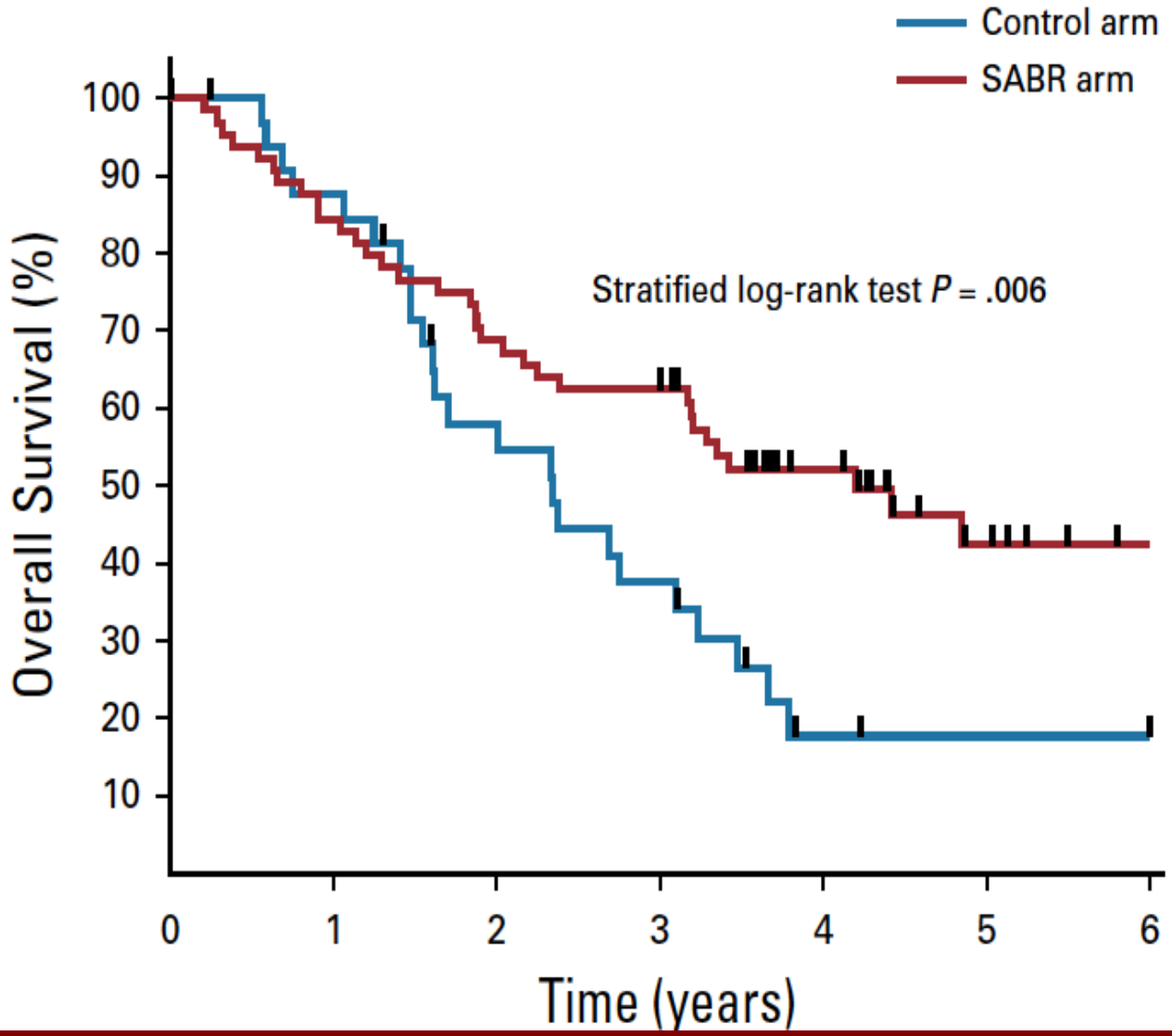
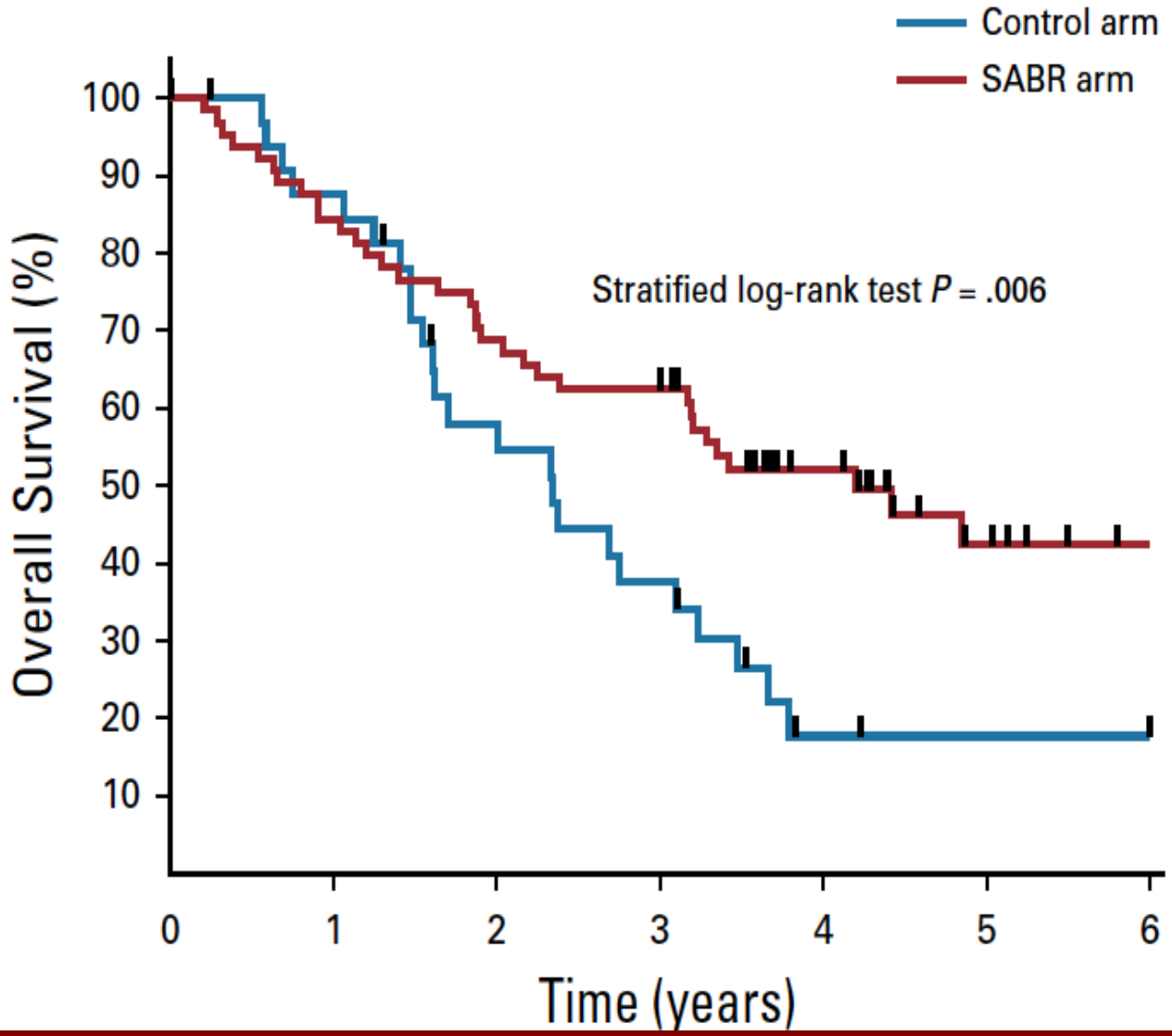
SABR-COMET:
SBRT *Improves Survival* (Phase II screening)



SABR Improved Median Survival from 28 to 41 months

SABR-COMET:
SBRT *Improves Survival* (Phase II screening)



4.5% Grade 5 Toxicity

18 of 99 enrolled patients had breast cancer

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Advancing Research. Improving Lives.™

NRG-BR002: A Phase IIR/III Trial of Standard of Care Systemic Therapy with or without Stereotactic Body Radiotherapy (SBRT) &/or Surgical Resection (SR) for Newly Oligometastatic Breast Cancer (NCT02364557)

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ASCO
6/4/2022

NRG-BR002 Schema: Phase IIR/III Design

OLIGOMETASTATIC BREAST CANCER

Controlled Locoregional Disease and ≤ 4 Metastases (***standard imaging***)
≤ 12 months systemic therapy without progression

STRATIFICATION

- Metastases (1 vs. >1)
- Hormone receptor status (ER+ and/or PR+ vs. ER- and PR-)
- HER2 status (Positive vs. Negative)
- Chemotherapy for MBC (Yes vs. No)

RANDOMIZATION 1:1

Targeted Accrual:
Phase IIR: 128
Phase III: 360 (Ph IIR + 232)

ARM 1

Symptom directed palliative therapy as needed

Standard ***systemic*** therapy

ARM 2

Total **ablation** of all metastases

Standard ***systemic*** therapy

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Statistical Design

Phase IIR (n=128):

- **Hypothesis**: Metastasis-directed therapy of all ***VISIBLE*** lesions with systemic therapy will provide a **signal** for improved ***PFS*** (hazard ratio [HR]=0.55, corresponding to median PFS from 10.5 to 19 months).

  → Failure defined as: progression of metastases, new metastases, or death

  → Log-rank test statistic; 1-sided significance level = 0.15 (70% CI); 92% power; 69 events

  → If PFS "Go Signal", trial continues to answer Ph III overall survival (OS)

SBRT / SABR Dosing and Quality Assurance

Metastatic Location	Dose (60-90% IDL)	Biologic Dose (Breast Cancer)
Lung - Peripheral	45 Gy 3 fractions	230 Gy
Lung - Central	50 Gy 5 fractions	192 Gy
Mediastinal/ Cervical LN	50 Gy 5 fractions	192 Gy
Liver	45 Gy 3 fractions	230 Gy
Para/Spinal	30 Gy 3 Fractions	115 Gy
Osseous	30 Gy 3 Fractions	115 Gy
Abdomen (LN / Adrenal)	45 Gy 3 fractions	230 Gy

- Derived from **NRG-BR001**
- Prospective data/expert consensus from NRG, Alliance, SWOG
- 1st patient for each metastatic site at an institution were reviewed in real time.*

* Except physicians passing NRG-BR001 credentialing

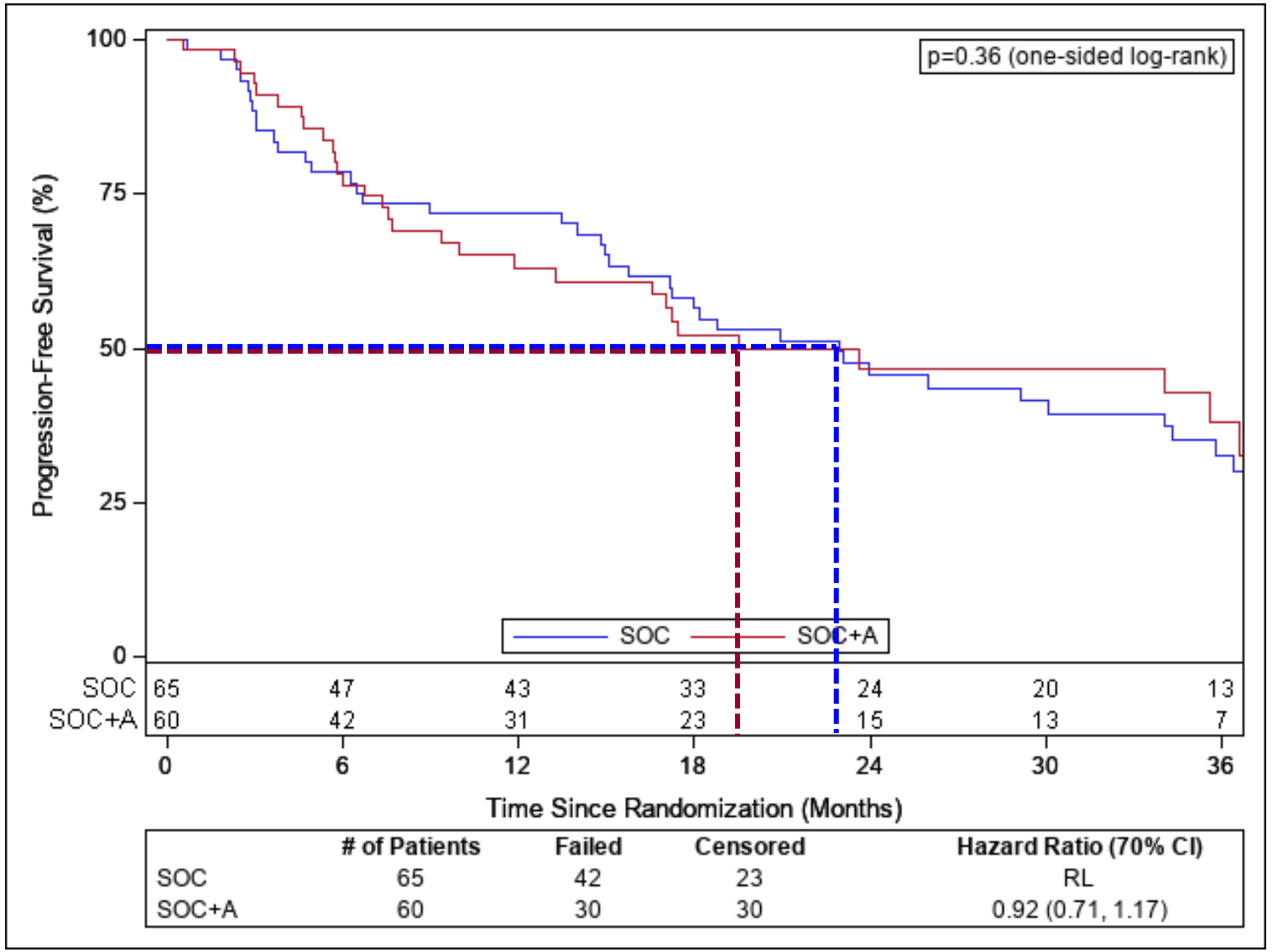
Patient and Tumor Characteristics

	Standard of Care (n=65)	Standard of Care + Ablation (n=60)	Total (n=125)
Age (years)			
Median	53	55.5	54
Performance Status (Zubrod)			
0	41 (63%)	41 (68%)	82 (66%)
1	24 (37%)	19 (32%)	43 (34%)
Patient Metastasis Count			
1	39 (60%)	36 (60%)	75 (60%)
>1	26 (40%)	24 (40%)	50 (40%)
Hormone Receptor/HER2 Status			
ER and PR-; HER2-	5 (8%)	5 (8%)	10 (8%)
ER and PR-; HER2+	2 (3%)	1 (2%)	3 (2%)
ER and/or PR+; HER2+	6 (9%)	7 (12%)	13 (10%)
ER and/or PR+; HER2-	52 (80%)	47 (78%)	99 (79%)
Metastatic Timing			
Synchronous	12 (18%)	15 (25%)	27 (22%)
Not synchronous	52 (80%)	45 (75%)	97(78%)
Pending	1 (2%)	0 (0%)	1 (1%)

Treatment

	Standard of Care (n=65)	Standard of Care + Ablation (n=60)	Total (n=125)
Ablation			
SBRT/SABR		56 (93%)	
Surgery		1 (2%)	
No protocol treatment		3 (5%)	
Systemic Therapy (1st Follow up)			
Chemotherapy	18 (28%)	16 (27%)	34 (27%)
Hormonal	54 (83%)	41 (68%)	95 (76%)
Biologic	48 (74%)	36 (60%)	84 (67%)
Bone Protective	21 (32%)	9 (15%)	30 (24%)
No protocol treatment	3 (5%)	3 (5%)	6 (5%)

Primary Endpoint: PFS



	SOC (n=65)	SOC+A (n=60)
24-month estimate (70% CI)	45.7% (38.9%, 52.5%)	46.8% (39.2%, 54.3%)
36-month estimate (70% CI)	32.8% (26.0%, 39.5%)	38.1% (29.7%, 46.6%)
mPFS		
Design	10.5 months	19 months
Observed	**23 months**	**19.5 months**

HR [SOC+A/SOC] (70% CI): 0.92 (0.71, 1.17)

Median Follow-up = 35 months
(min-max: 0.03-62.74)

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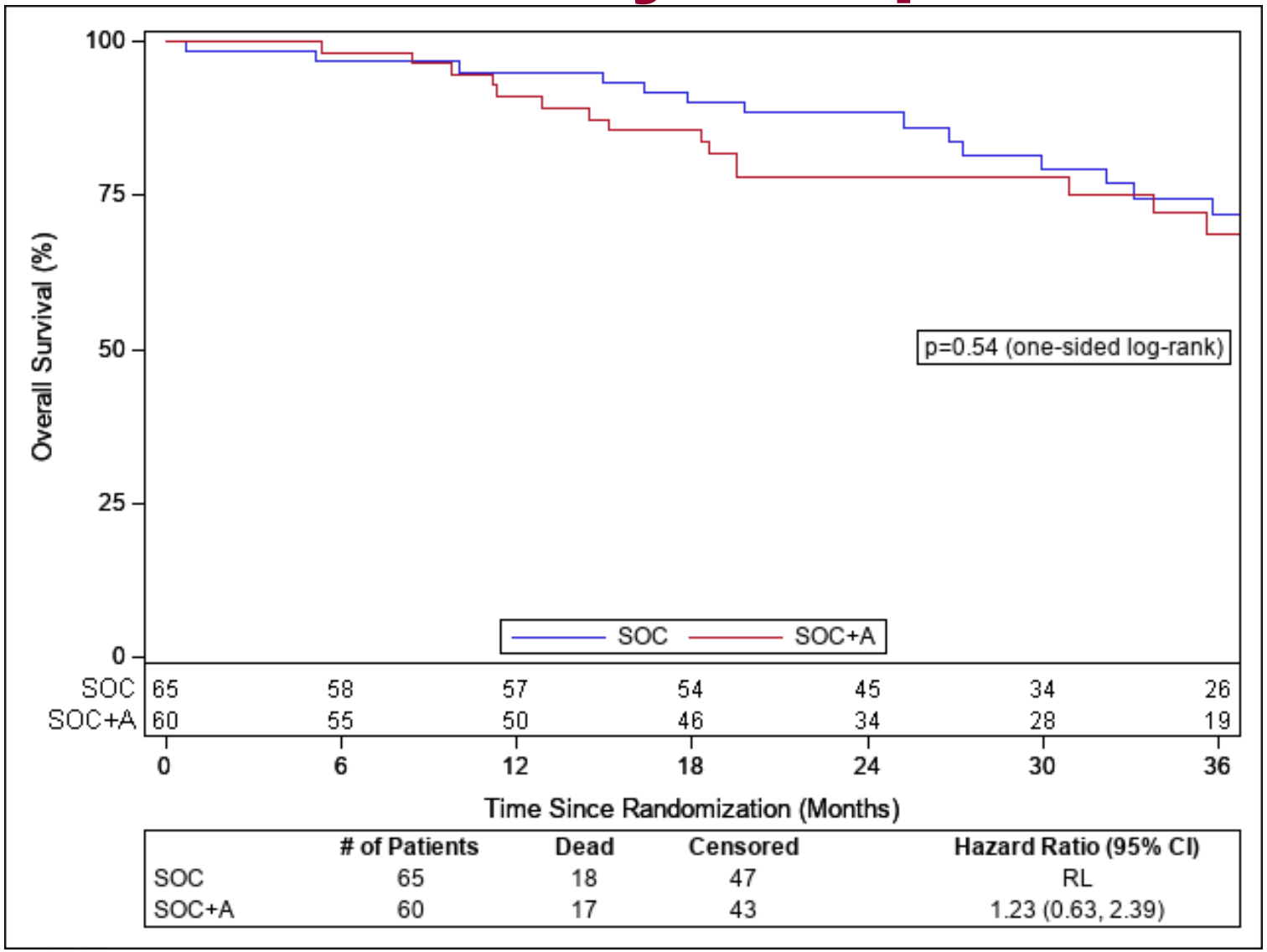
Secondary Endpoint: Overall Survival

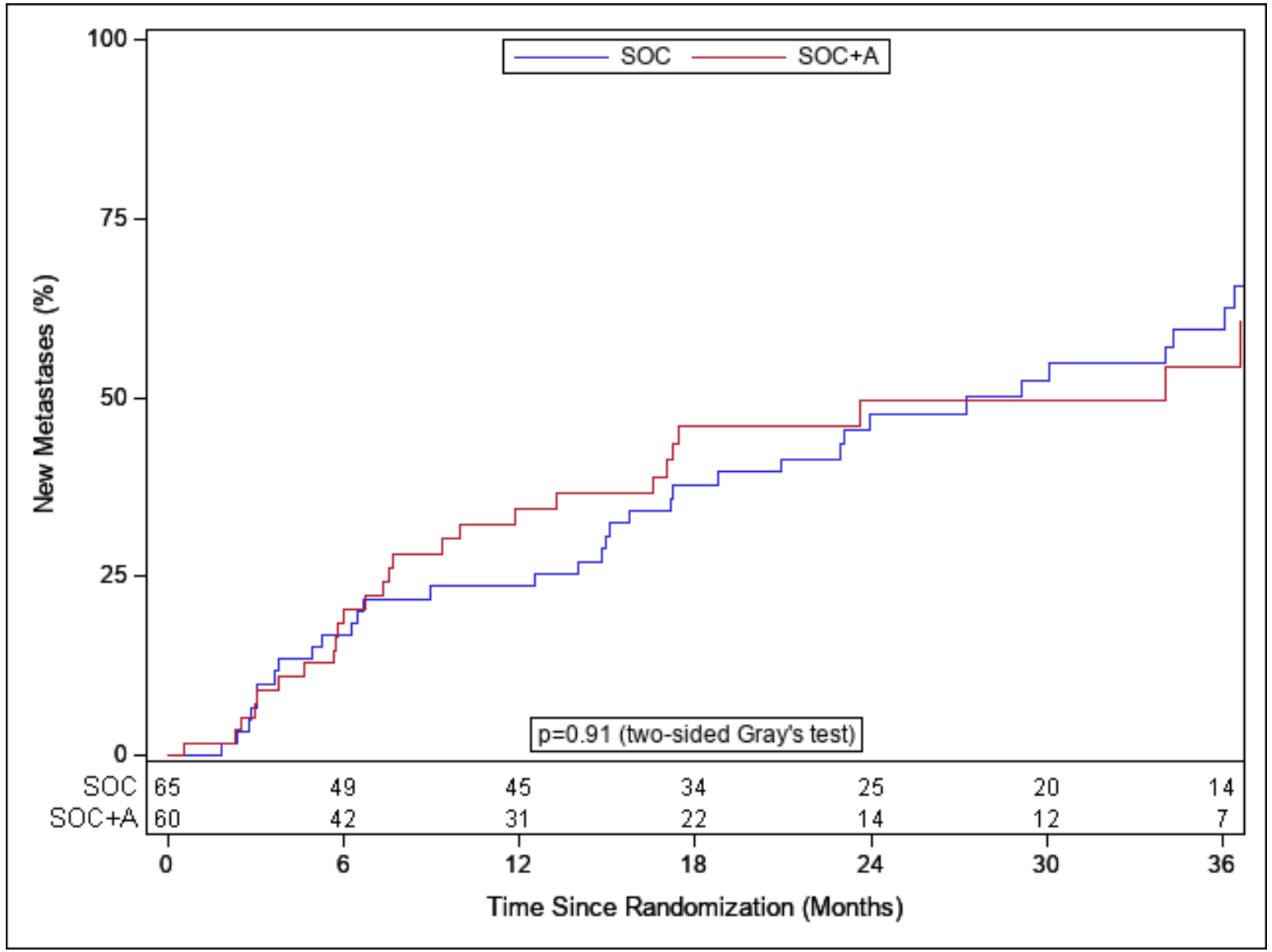


	SOC (n=65)	SOC+A (n=60)
36-month estimate (95% CI)	**71.8%** (58.9%, 84.7%)	**68.9%** (55.1%, 82.6%)

HR [SOC+A/SOC] (95% CI): 1.23 (0.63, 2.39)

OS time is measured from the date of randomization to the date of death or last follow-up

New Metastases & Patterns of 1st Failure



Analysis of first failure:

- New mets *outside* index area (Arm 1) /RT field (Arm 2)
  - Developed similarly in both arms (~40%)
- New mets *inside* index area (Arm 1) /RT field (Arm 2)
  - Fewer for SOC+A: 7% vs. 29%

Toxicity and Quality Assurance

Highest Grade Adverse Event
Definitely, Probably, or Possibly Related to Protocol Treatment

	Standard of Care (n=62)					Standard of Care + Ablation (n=57)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
Overall Highest Grade	1	2	3	4	5	1	2	3	4	5
	13	17	6	1	0	18	16	3	0	0
	(21)	(27)	(10)	(2)	(0)	(32)	(28)	(5)	(0)	(0)

NRG BR002 Conclusions

- Patients with Oligometastatic breast cancer as defined by NRG-BR002 have long PFS and OS.

- High dose SBRT was safe with low rates of treatment-related adverse events, similar to the standard of care arm owing to the quality assurance and metrics.

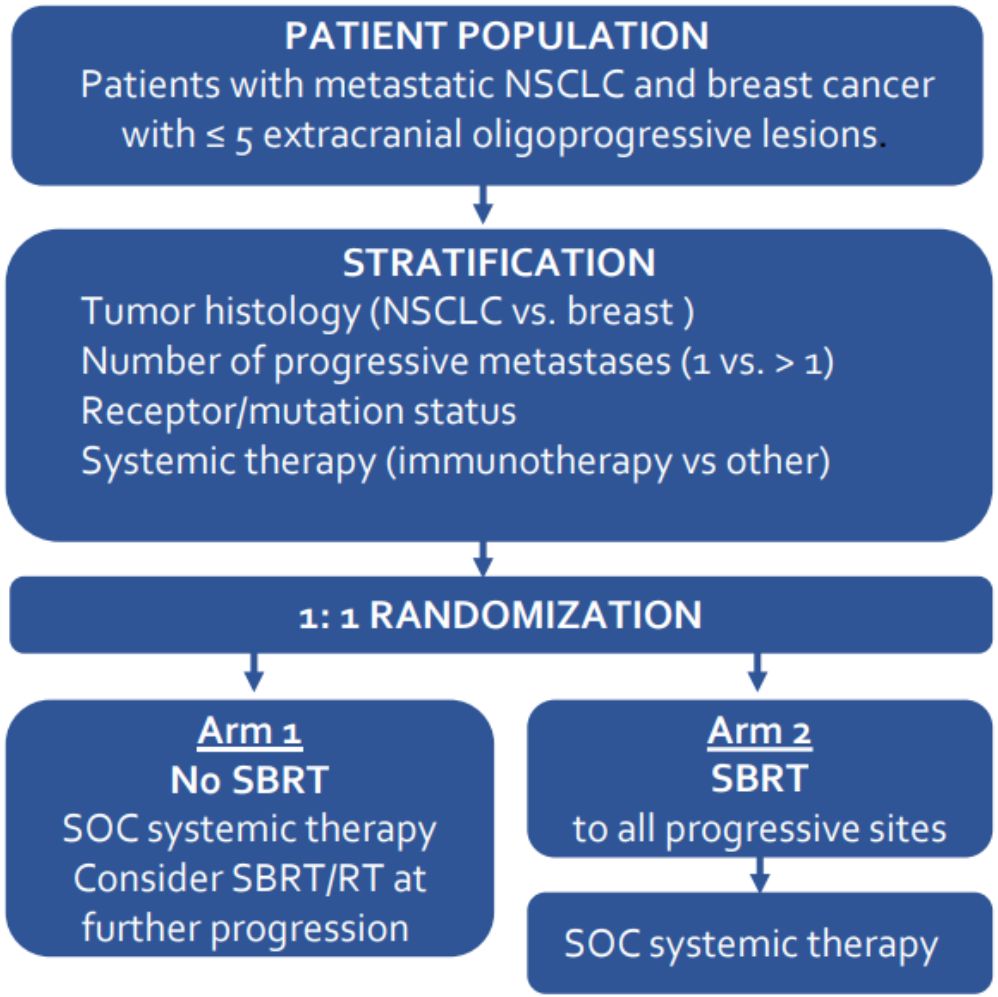
- Metastatic-directed therapy ***failed to improve PFS*** for patients with Oligometastatic breast cancer.

Therefore, there is a "No-Go Signal" to continue accrual to answer the Phase III OS question.

Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression

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

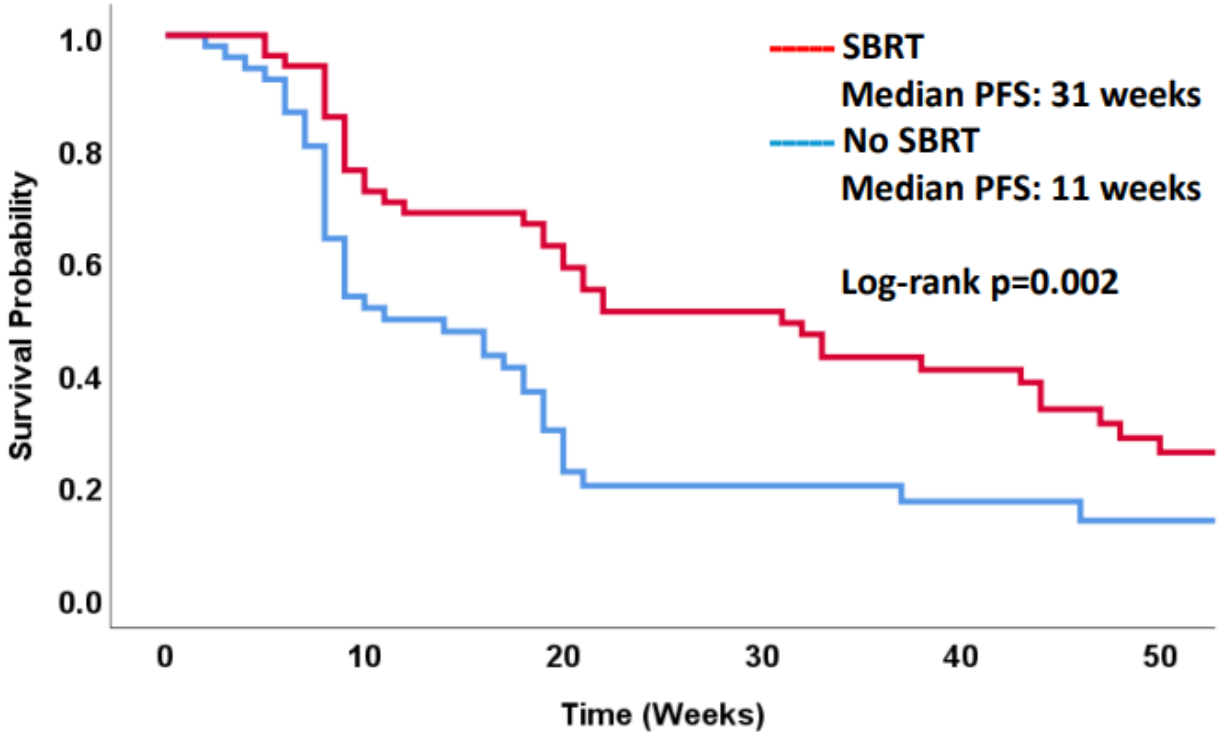


SBRT Doses:
9-10 Gy x 3 fxns or
10 Gy x 5 fxns

Tsai et al. ASTRO Annual Meeting, 2021

CURB Results

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.

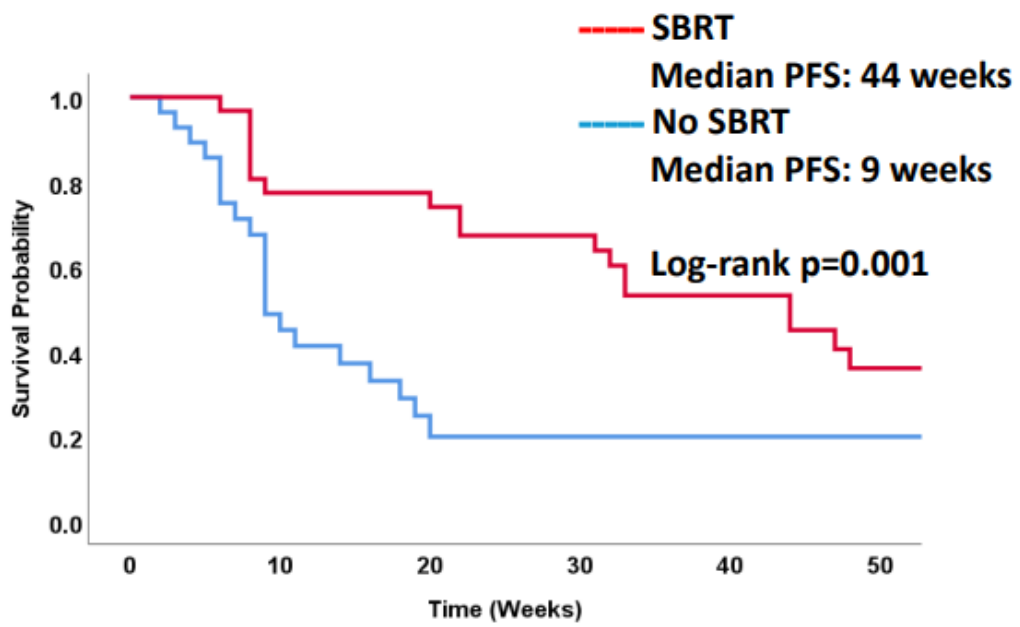
39 of 106 (37%) died.

Tsai et al. ASTRO Annual Meeting, 2021

CURB Results

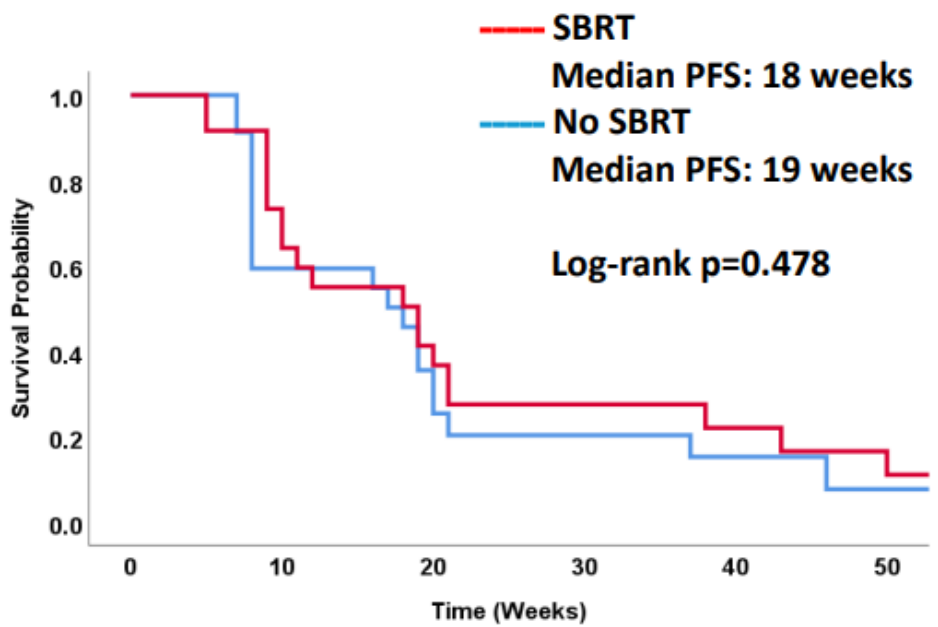
Results – PFS by Primary Disease Sites

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)

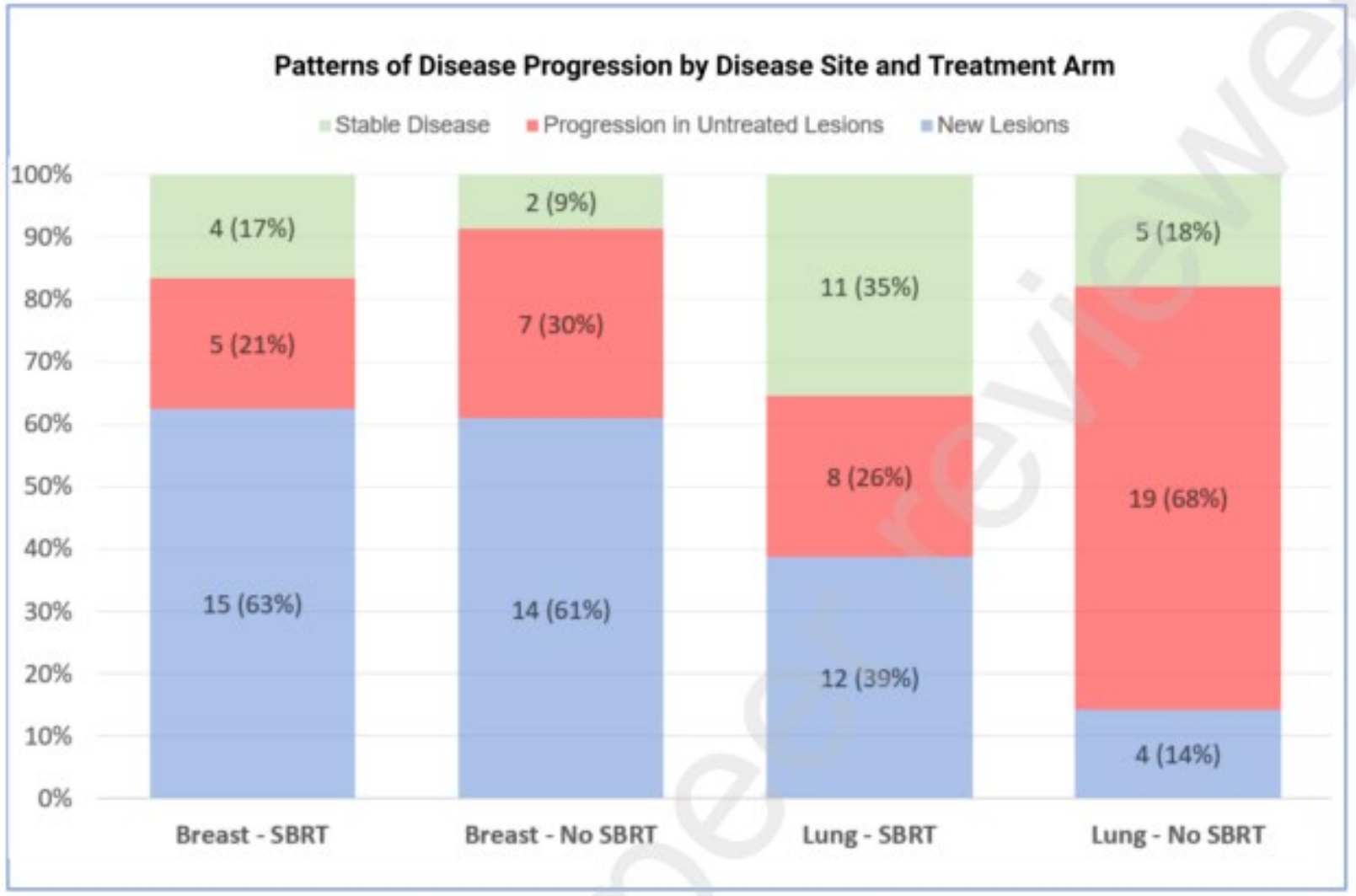


Number at risk						
SBRT	24	15	8	6	4	2
No SBRT	23	13	6	4	3	1

Tsai et al. ASTRO Annual Meeting, 2021

CURB Results

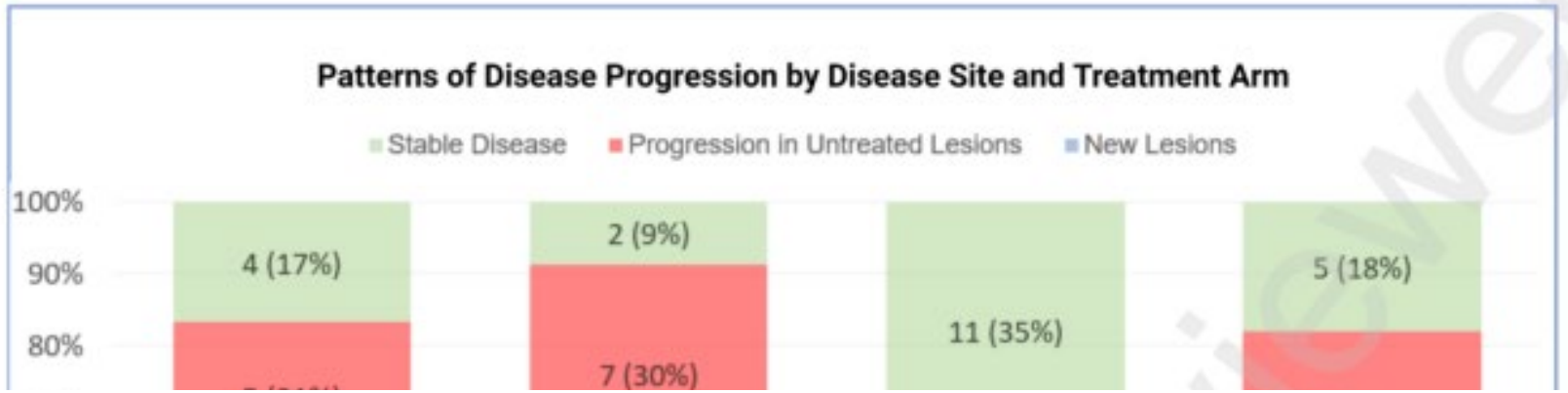
Figure 3B. Patterns of Disease Progression by Disease Site and Treatment Arm



Tsai et al. Lancet pre-print, 2023

CURB Results

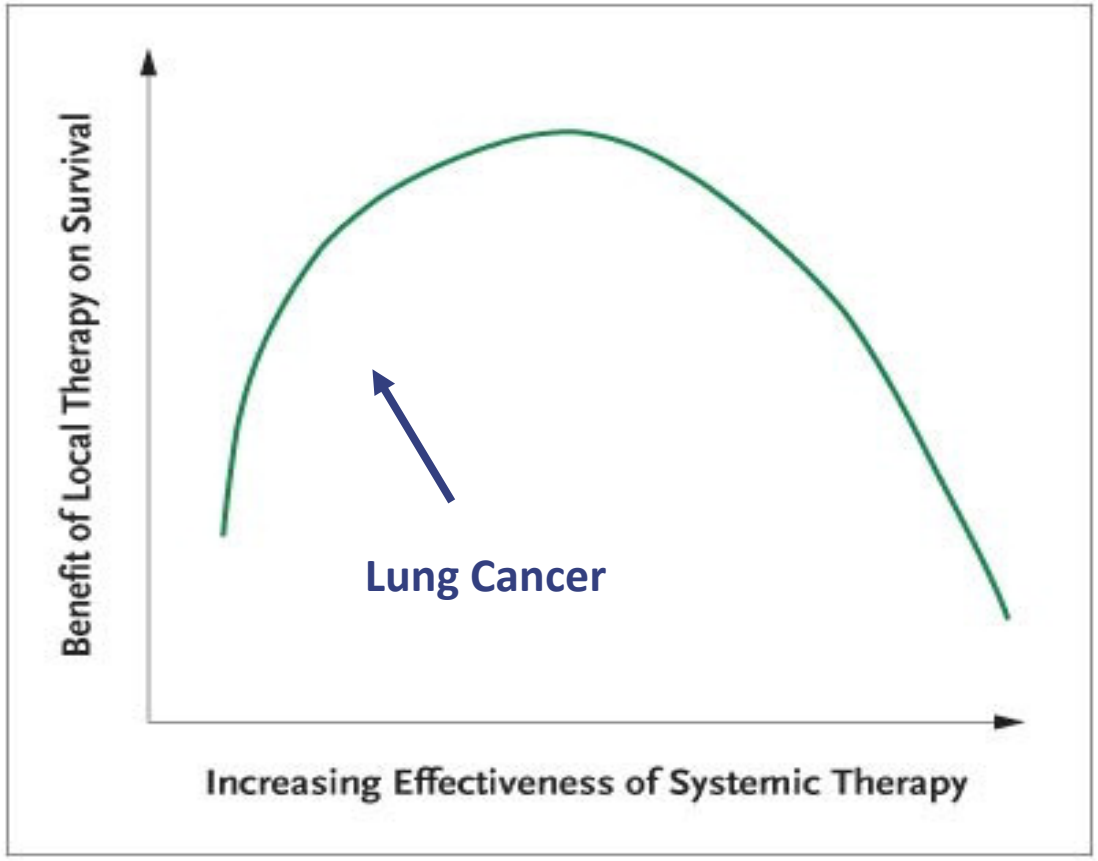
Figure 3B. Patterns of Disease Progression by Disease Site and Treatment Arm



In Breast Cancer, SBRT does <u>not</u> prevent progression of untreated lesions or prevent development of new metastatic lesions

Tsai et al. Lancet pre-print, 2023

Hypothetical Benefit of Improved Local Tumor Control with Increasing Effectiveness of Systemic Therapy



Punglia RS et al. *N Engl J Med.* 2007;356(23):2399-2405.

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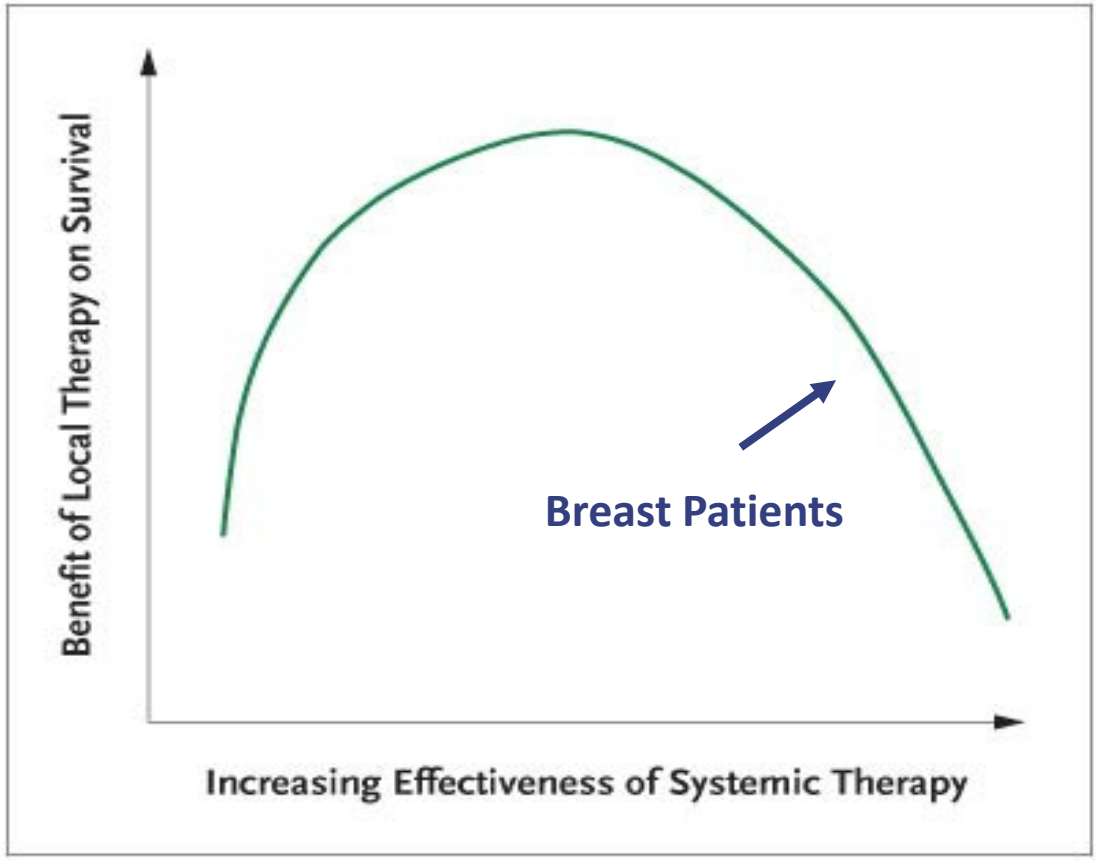

Punglia RS et al. *N Engl J Med.* 2007;356(23):2399-2405.

Conclusions

- SBRT ablative treatment to oligometastasis in breast cancer patients does not prolong survival
- SBRT ablative treatment does not improve progression free survival in patients with oligoprogressive breast cancer

Take Home

There is no role for SBRT in patients with oligometastatic breast cancer

Acknowledgements

- Patients
- Steven J. Chmura, M.D., Ph.D.
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Thank you!