

De Novo Metastatic Breast Cancer and the Role of Surgery

Terry Mamounas, M.D., M.P.H., F.A.C.S.

Medical Director, Breast Program and Research Activities

AdventHealth Cancer Institute

Professor of Surgery, University of Central Florida College of Medicine

Clinical Professor of Clinical Sciences,

Florida State University College of Medicine

Primary Surgical Therapy in Pts with De Novo Stage IV BC

- Conventional wisdom is that once metastases have occurred, **aggressive local therapy provides no survival advantage** and should not be pursued except **to prevent local complications** (bleeding, ulceration, infection)
- Several retrospective studies have shown significantly **better outcomes** for women who had **surgical removal** of their tumor vs. those who did not (particularly for those who had **negative margins**)

Primary Surgical Therapy in Pts with De Novo Stage IV BC

- Most studies adjusted for imbalances in **known prognostic factors** (such as number of mets, location of mets, type of systemic therapy or use of radiotherapy)
- Most studies concluded that **unrecognized selection bias** may have accounted for the observed benefit of surgery and **only large prospective RCTs** could reliably answer the question

Tata Memorial Center Randomized Phase III Trial

Stage IV BC At Presentation

**Anthracyclines
+/- Taxanes
(CR /PR)**

R

N=350

**Loco-
Regional
Treatment***

**No Loco-
Regional
Treatment**

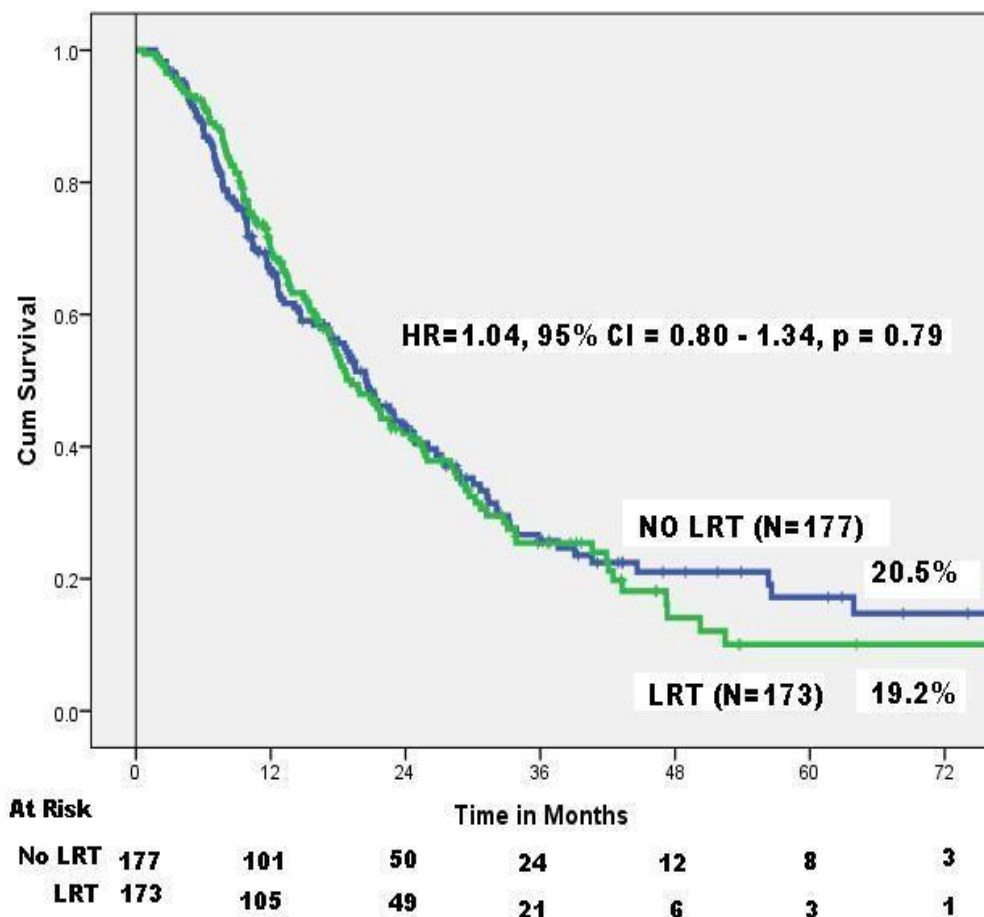
Stratification by:

- **Hormone-Receptor Status**
- **Site of metastases (visceral vs. bone vs. both)**
- **Number of metastatic lesions (< 3 vs. > 3)**

***LRT: BCS or Mastectomy + AND followed by radiation therapy (RT), as per standard adjuvant guidelines**

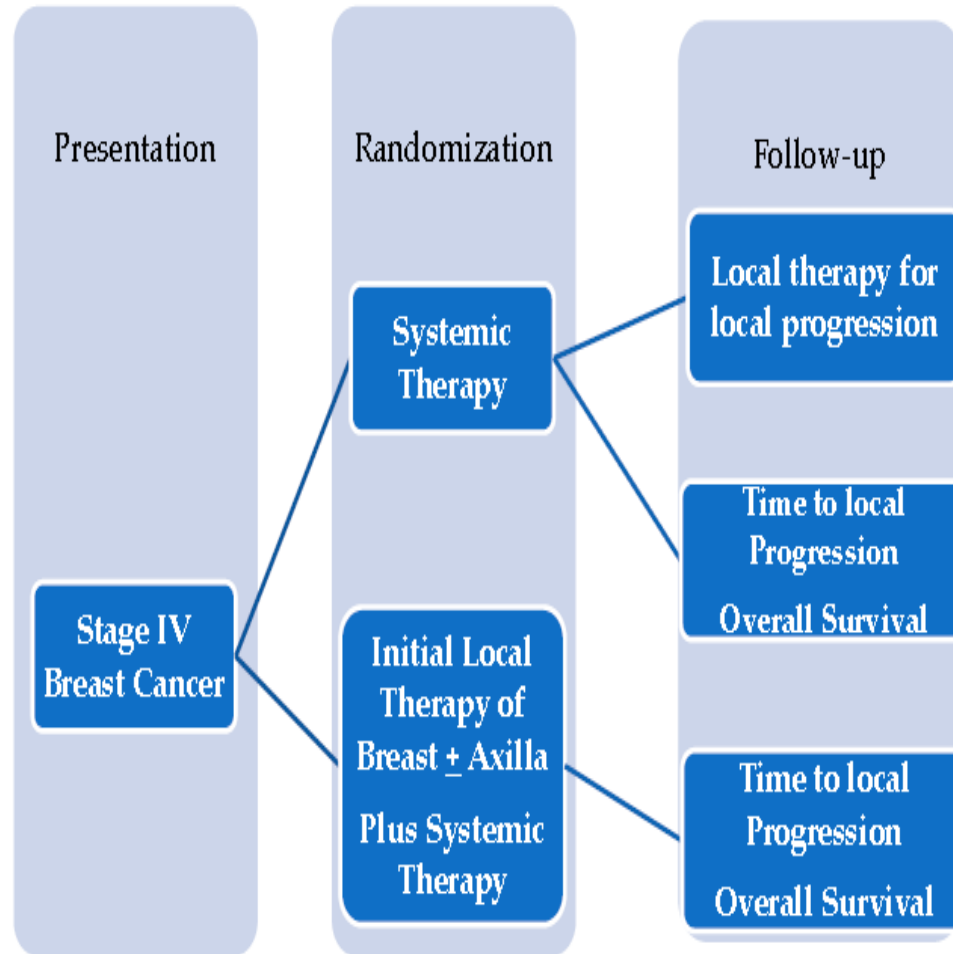
**Median F/U:
17 mos**

Tata Memorial Center Phase III Trial: Overall Survival



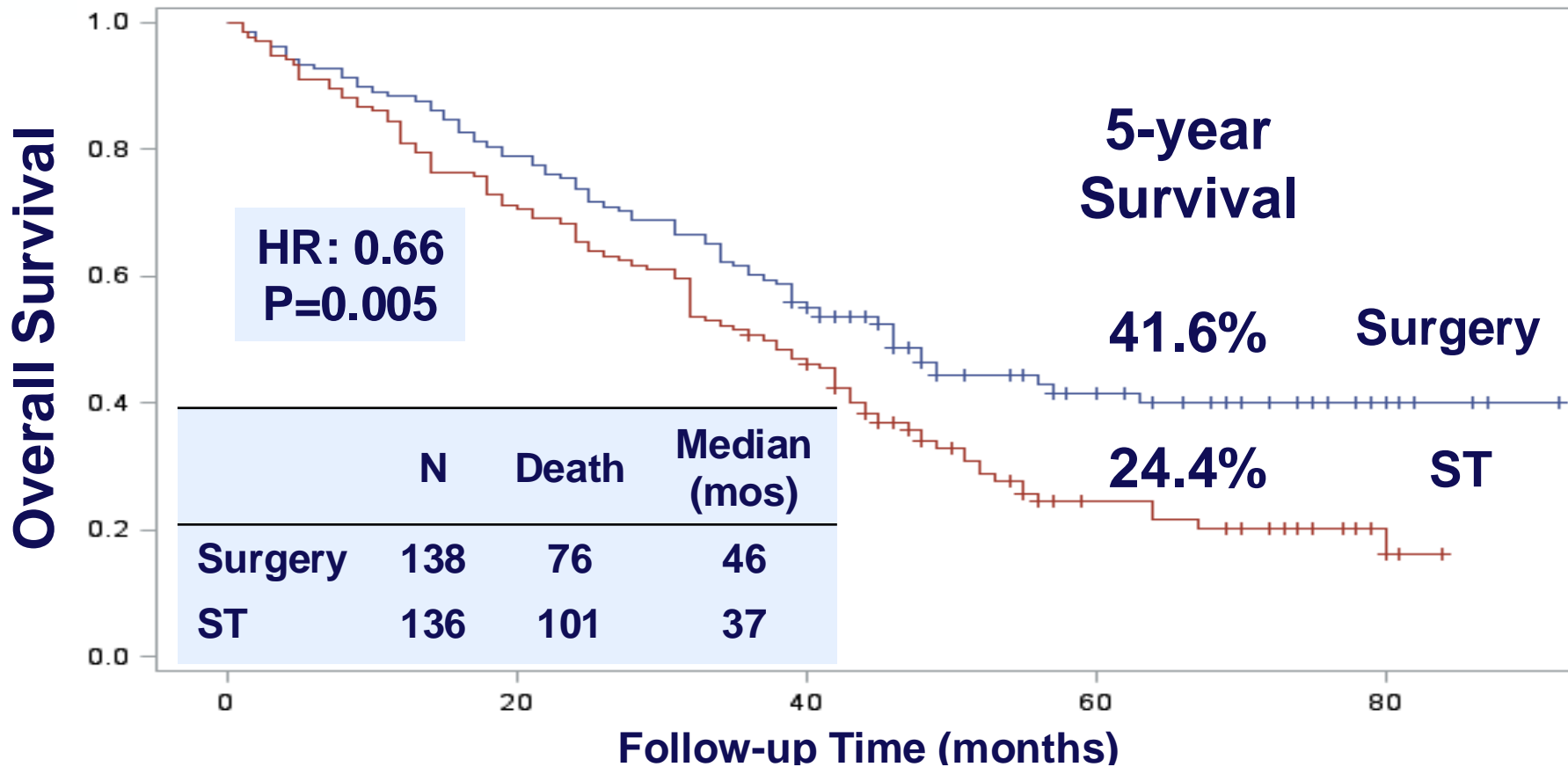
- The median OS in LRT and No-LRT arms were **18.8** and **20.5** months (HR=1.04, p=0.79)
- Corresponding 2-year OS were **40.8%** and **43.3%**, respectively
- No significant difference in OS between the two groups after adjusting for age, ER status, HER2 status, site and **number of mets** (HR=1.00, 95%CI=0.76-1.33, p=0.98).
- **89 (25%) patients had ≤ 3 metastatic lesions.** In these potentially oligometastatic patients, there was **no benefit of LR treatment** (HR = 1.16, CI 0.69; 1.95).

MF07-01 Turkish Study: Design



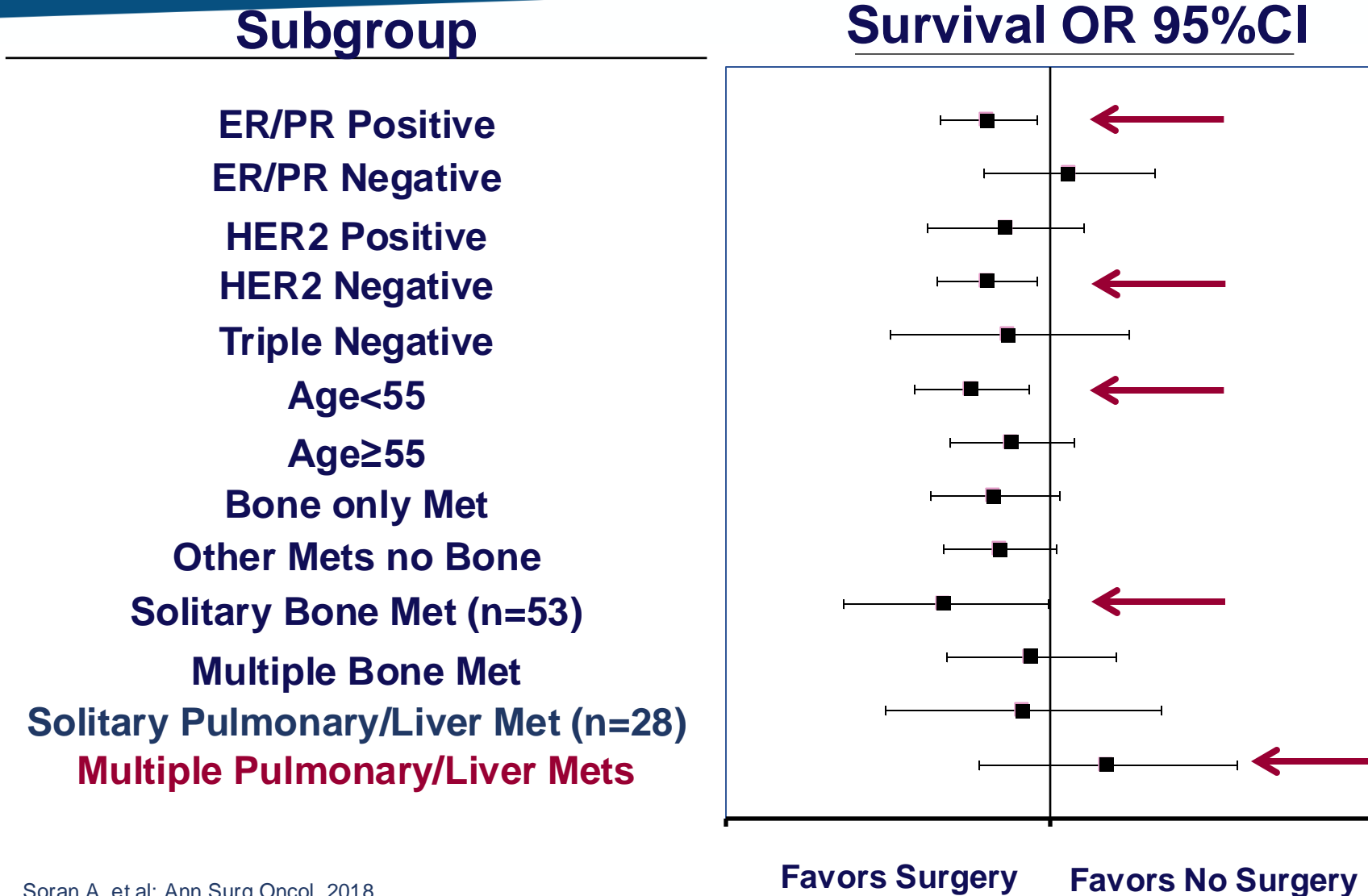
- **Chemotherapy** to all patients either after randomization in the ST treatment arm or after surgical resection the surgery arm
- **Hormone therapy** for **HR positive BC** and **trastuzumab** for **HER-2 positive BC**
- **Surgery-RT** at discretion of investigator

MF07-01 Turkish Study: 5-Year Overall Survival



Number at Risk	Surgery	ST
0	138	136
20	109	97
40	75	63
60	27	17
80	6	5

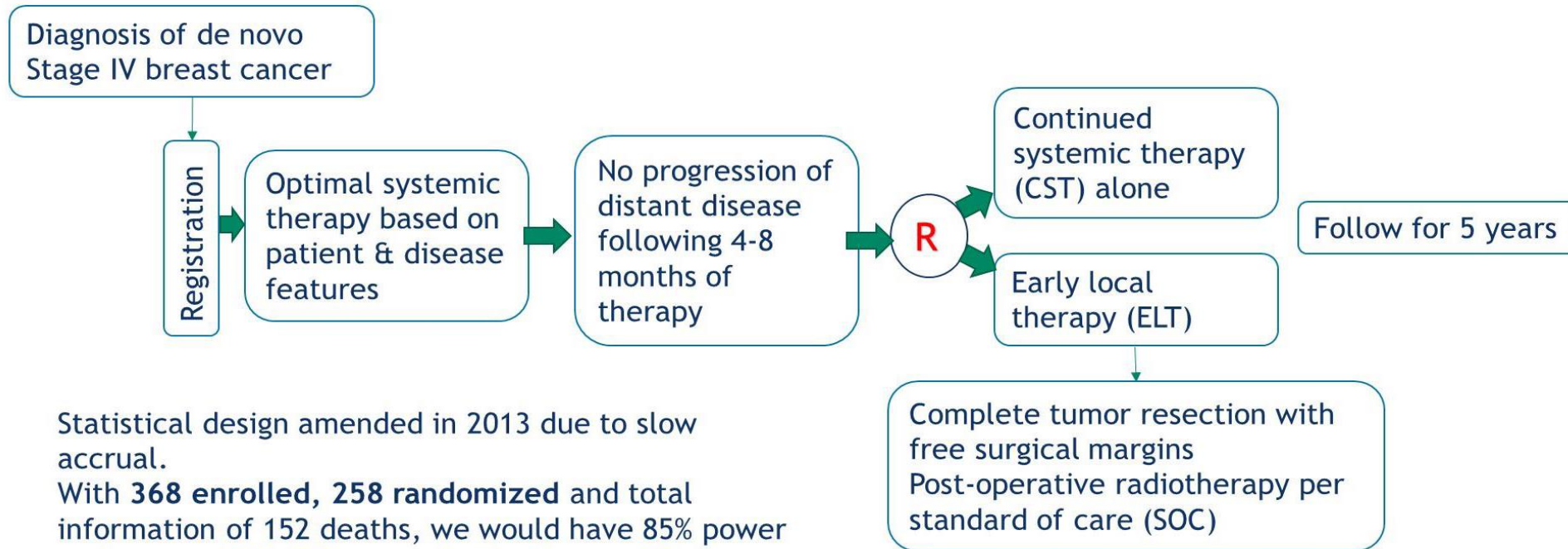
MF07-01 Turkish Study: 5-Year Overall Survival



ECOG-ACRIN E2108: Design

Design of E2108

Opened in 2011, last patient enrolled in 2015.

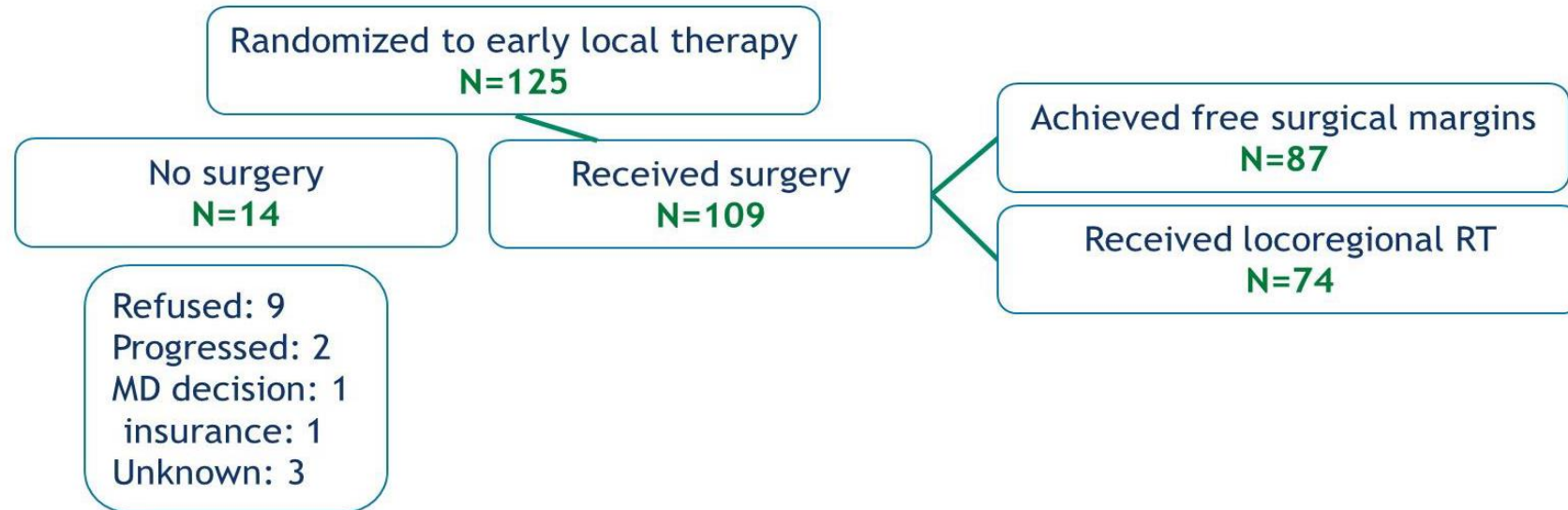


Statistical design amended in 2013 due to slow accrual.
With **368** enrolled, **258** randomized and total information of 152 deaths, we would have 85% power to detect a **19%** difference in the 3-year OS rates

Primary Endpoint: Overall Survival

ECOG-ACRIN E2108: LR Therapy

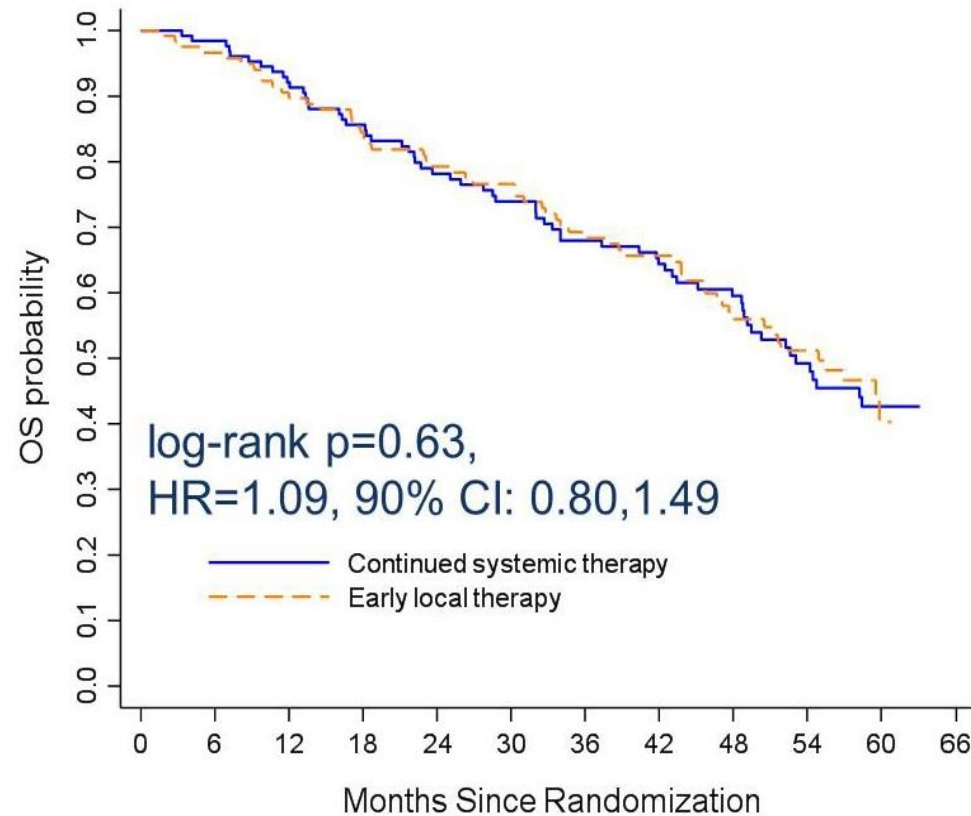
Delivery of locoregional therapy in early local therapy arm



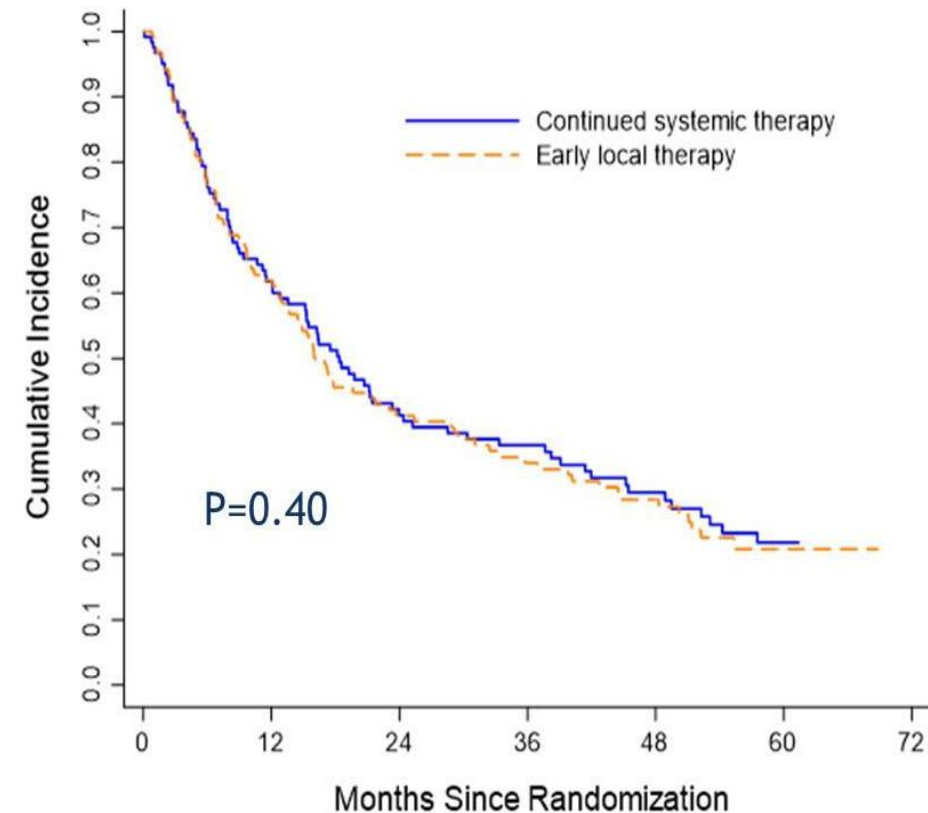
- In the systemic therapy arm, 25 women received surgery: 13 in the year following randomization and 12 at a later time.

ECOG-ACRIN E2108: Results

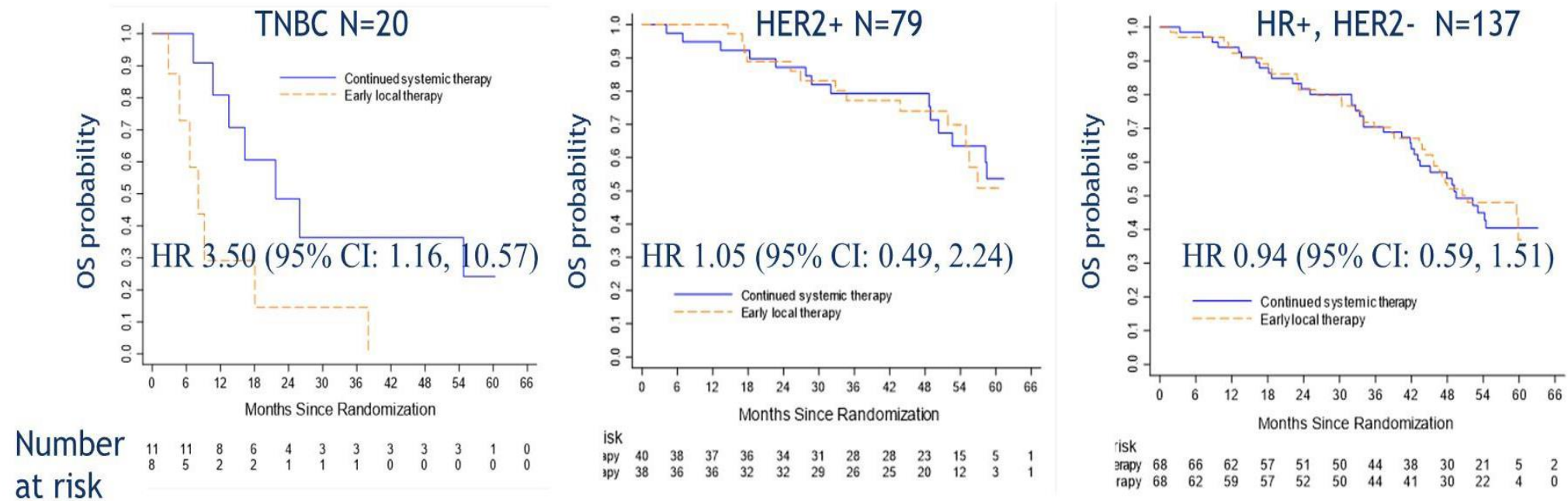
Overall Survival



Progression-Free Survival

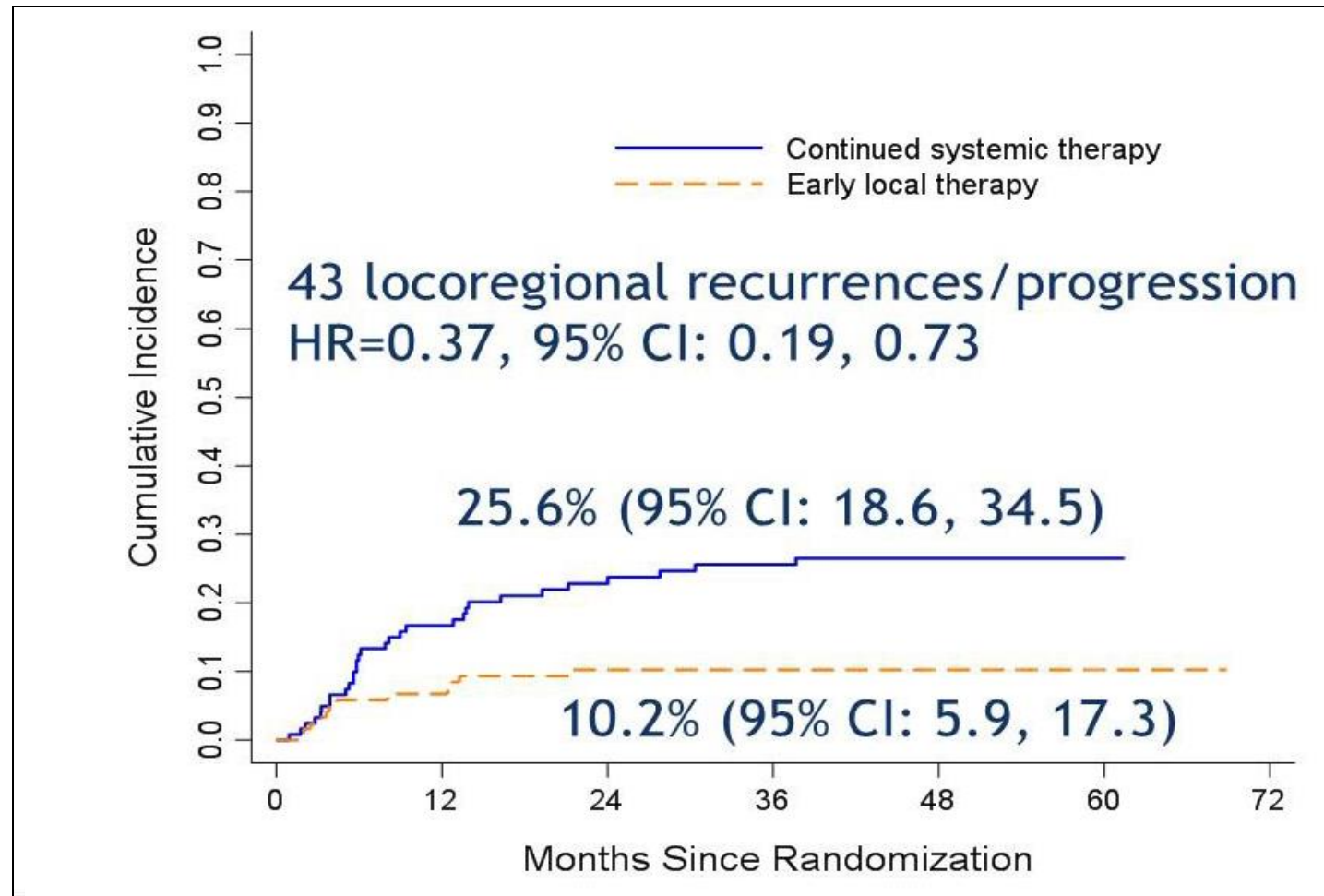


ECOG-ACRIN E2108: Overall Survival by Subtype



- For 20 women with TNBC, survival was worse in the early local therapy arm.

ECOG-ACRIN E2108: Loco-regional Progression



Primary Surgical Therapy in Pts with De Novo Stage IV BC

- **Not removing the primary tumor** remains the **standard** in pts with **de novo stage IV disease**
- **Surgery** can be entertained in selected cases for **local control** if local tumor manifestations are more likely to contribute to morbidity than distant ones
- In such cases, **BCS** is preferable if it can encompass the scope of the surgical resection
- **Axillary node surgery** or **breast XRT** are **generally not advisable**

Metastasis-Directed Therapy in Patients with Oligometastatic Breast Cancer

What Is Oligometastatic State?

- The oligometastatic state was first described by **Hellman and Weichselbaum** based on the spectrum theory of cancer spread
- They postulated the existence of a **clinically distinct, intermediate stage** between LR confined disease and widespread distant mets
- In this stage, the disease may have a **more indolent biology** compared to later in the metastatic cascade
- They hypothesized that **treatment of all known cancer** (both primary and mets) could lead to **long disease-free interval and potentially even cure**

Definition and Incidence of OMBC

- OMBC is characterized by **single/few detectable metastatic lesions**
- The 3rd ESO-ESMO Consensus Guideline for Advanced Breast Cancer (ABC 3) defined OMBC as **disease confined to a solitary organ** or low volume metastatic disease with **limited number and size of metastatic lesions (≤ 5 but not necessarily in the same organ)**
- Reported to represent up to **20%** of Stage IV patients
- Among patients with MBC in major phase II/III clinical trials of systemic therapy, **about 50%** present with **≤ 2 clinically detected metastases**

Therapeutic Strategy for OMBC

- **ASTRO-ESTRO** and **ESO-ESMO** recommend a **curative treatment strategy**, when possible, for OMBC
- **ASCO** has made **recommendations**, but limited to **patients with 1-4 CNS metastases of HER2-positive breast cancers**
- Although the **benefits of aggressive strategy** have not yet been clearly demonstrated, most studies seem to confirm the **feasibility and relative safety of focal treatments** (surgery, SBRT or percutaneous image-guided treatment)

Arguments Against Multidisciplinary Rx for OMBC

- **No study** has formally demonstrated this benefit (except Phase II SABR-COMET)
- Retrospective analyses have **selection bias**
- Dangerous to implement aggressive strategies for patients with indolent and low burden disease for whom **prolonged survival** may be related to the **nature of the disease itself**
- Arguments in favor of an **OMBC specific genotype** are based on **little preclinical or clinical data supporting** this hypothesis
- **Focal treatment** of a primary tumor in patients with MBC **may have a negative impact**
- **Surgery and anesthesia** may also increase **immunosuppression**

Surgical Treatment for Oligometastases

- Large series of resection of lung, liver, adrenal, and brain metastases have demonstrated better-than-expected long-term disease control and survival for select patients:
 - Based on **complete vs. incomplete resection**
 - Based on **preoperative disease response/stabilization with systemic therapy vs. disease progression**
- Favorable outcomes of BC patients undergoing resection of brain and bone metastases have also been reported
- While still controversial, **rates of metastasectomy** have been **increasing** across all cancer sites in recent years

Hepatic Metastasectomy for OMBC

- Only **4% to 5%** of MBC patients have solitary **isolated liver mets**
- Patients with liver mets have a **worse OS** compared to those with bone-only disease (**3-year OS rate of around 38%**)
- **Surgery** has been reported to **prolong OS** in patients with isolated liver mets with **>2 years OS** in patients with **good response to ST** and **negative surgical margins**
- Hepatic metastasectomy:
 - Median mortality: **0%-5.9%**
 - Median morbidity: **15%-20%**
 - 5-year survival rate: **40%**
 - Median OS: **36 mos (12-58)**
- Radiofrequency ablation (**RFA**) is safe for **solitary lesions <3 cm** with **effective local control and minimal mortality risk**

Pulmonary Metastasectomy for OMBC

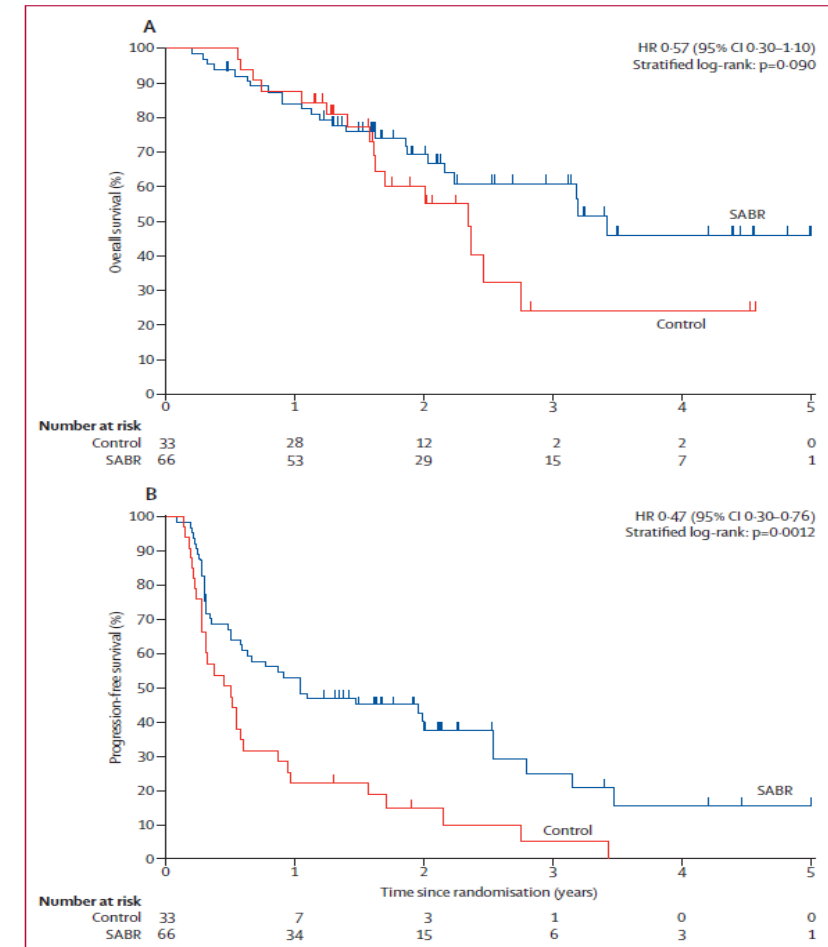
- **15%-24%** of MBC patients have **isolated lung or pleural space mets**
- Resection may have diagnostic and therapeutic utility
- Systematic review and meta-analysis of cohort studies:
 - **16 studies** including **1937 patients**
 - Pooled 5-year survival rates: **46%** (95% CI: 43-49%).
 - Poor prognostic factors were:
 - **Disease-free interval (DFI) <3 years**; HR =1.70 (95% CI: 1.37-2.10),
 - **Incomplete resection of metastases**; HR =2.06 (95% CI: 1.63-2.62)
 - **Number of pulmonary metastases >1**; HR =1.31 (95% CI: 1.13-1.50)
 - **Negative HR status of metastases**; HR =2.30 (95% CI: 1.43-3.70).

Radiation Treatment for Oligometastases

- Radiation therapy has been used to treat OMBC
 - Stereotactic body radiation therapy (SBRT)
 - Stereotactic ablative radiation therapy (SABR)
 - Hypofractionated image-guided radiation therapy (HIGRT)
- Numerous studies have shown **high control rates** of metastases with acceptable toxicities for **lung, liver, adrenal, and multi-site HIGRT**
- Use of HIGRT to treat OMD has increased over time
- International survey of > 1,000 radiation oncologists:
 - **60% treat OMD with HIGRT (59% of the remaining planned to start)**

SABR-COMET Randomized Phase II Trial of SBRT

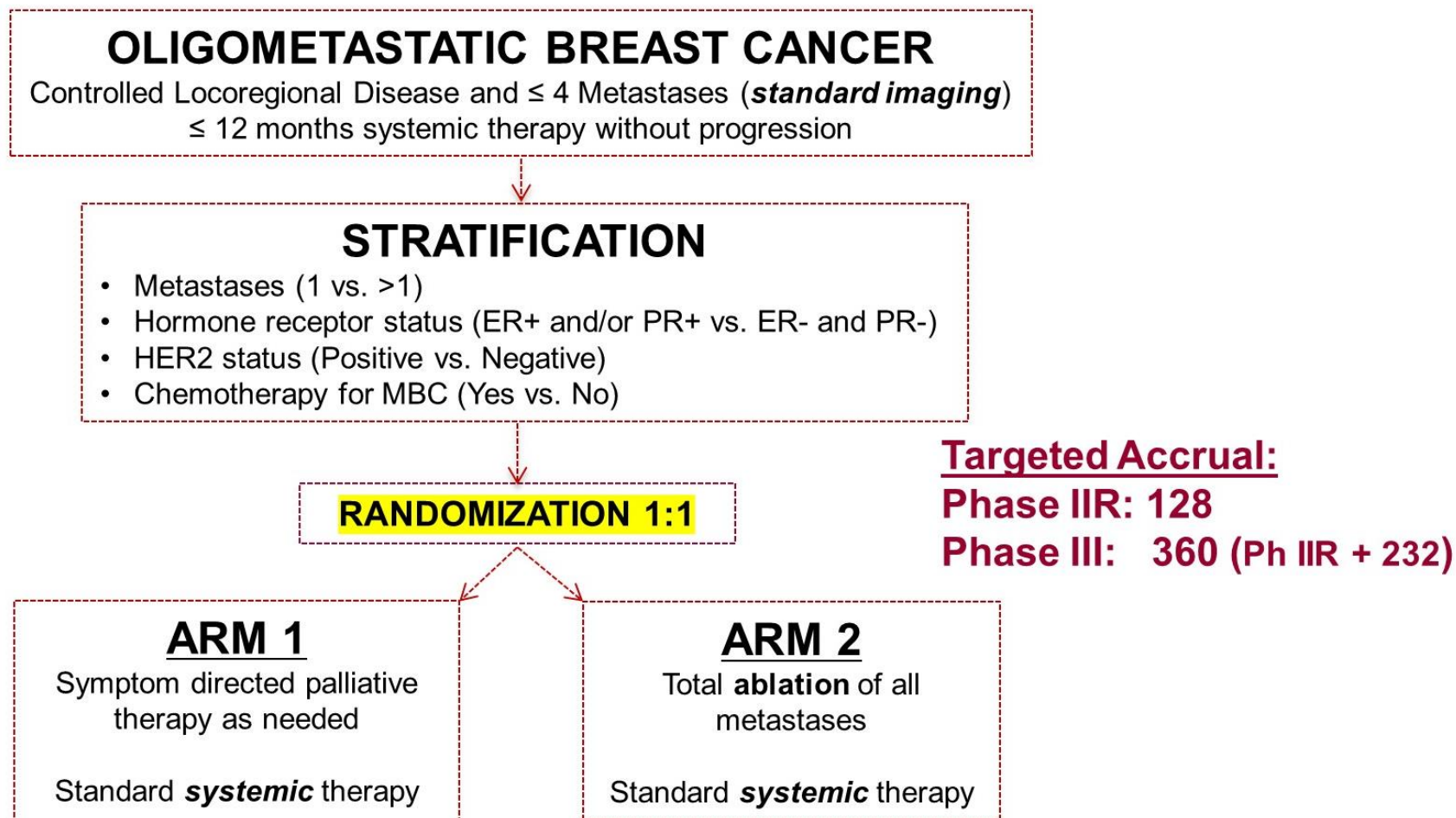
- Assessed **standard treatment +/- SBRT** in patients with **controlled primary tumor** who had **≤ 5 metastatic lesions**
- The study enrolled **99 patients** with **different tumor types**
- **18 patients** had a **breast cancer primary**
- **93%** of patients had **1-3 lesions**
- **SBRT significantly increased median PFS (12 vs 6 months, $P = 0.001$) and median OS (41 vs 28 months, $P = 0.09$)**



Randomized Phase II/III Trials of SBRT in OMBC

Trial	Randomization	# pts	Histology	Inclusion criteria	1° endpoint
NRG BR002 ⁹⁵	Ablative tx vs. Obs	128	Breast	1-4 non-CNS mets	OS
CORE ⁹⁶	HIGRT vs. SOC	245	Breast, NSCLC, prostate	Controlled 1° 1-3 mets	PFS
SABR-COMET-3 ⁹⁷	HIGRT vs. SOC	297	Any	1-3 mets	OS
SABR-COMET-10 ⁹⁸	HIGRT vs. SOC	159	Any	4-10 mets	OS

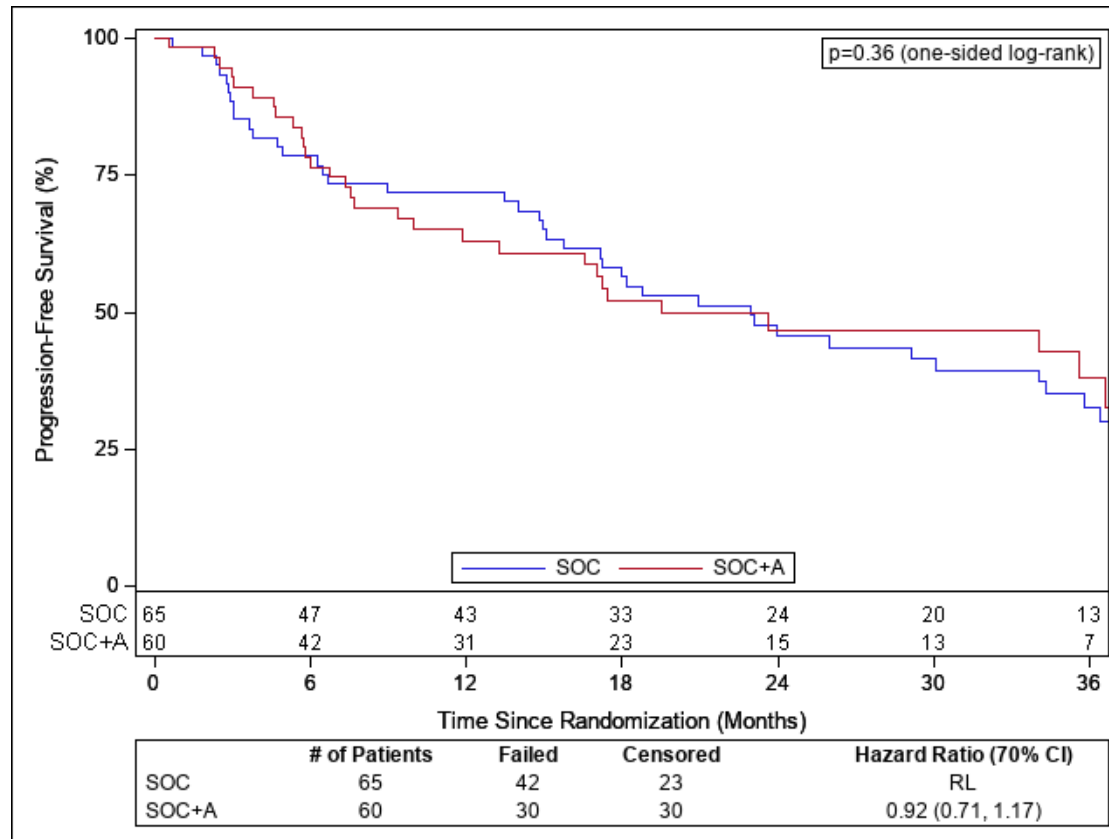
NRG-BR002 Schema: Phase IIR/III Design



NRG-BR002: Patient and Tumor Characteristics

	SOC (n = 65)	SOC + 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%)

NRG-BR002: PFS by Treatment Arm

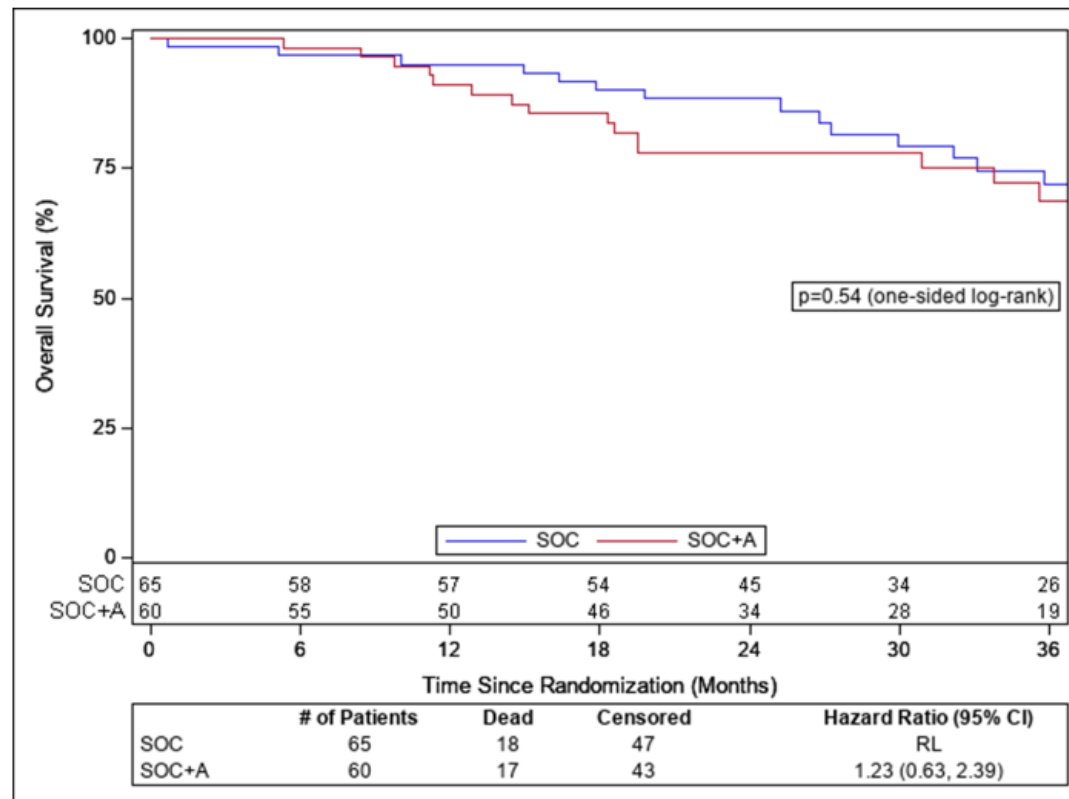


	SOC (n = 65)	SOC+A (n = 60)
24-month estimate (70% CI)	45.7% (38.9%, 52.5%)	46.8% (39.2%, 54.3%)
36-month estimate (70% CI)	32.8% (26.0%, 39.5%)	38.1% (29.7%, 46.6%)
mPFS		
Design	10.5 months	19 months
Observed	23 months	19.5 months

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

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

NRG-BR002: Overall Survival by Treatment Arm



	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)

NRG BR002: Conclusions

- Metastatic-directed therapy **failed to show signal for improved PFS** for patients with OMBC
- Therefore, there is a **“No-Go Signal”** to continue accrual to answer the **Phase III OS research question.**
- Patients with Oligometastatic breast cancer as defined by NRG-BR002 have **long PFS and OS**
- High quality/dose **SBRT was safe** with low rates of treatment-related adverse events, which were similar to the SOC arm.

Special Clinical Circumstances: Isolated Sternal Mets

- Isolated sternal mets may be related to the **close proximity of IM lymphatics to the sternum**
- This appears to be a **more favorable state** than even a solitary bone metastasis elsewhere
- **Case series** of sternal resection show **prolonged DFS and OS** compared to other metastatic populations
- A cohort study of 35 patients with de novo MBC with isolated sternal or mediastinal disease received curative-intent RT (≥ 50 Gy) in addition to surgery of the primary site and chemotherapy
- **5-year OS of 63%** and **5-year RFS of 52%**, (both **not different** from a comparator group of patients with **stage IIIC** disease)

Special Clinical Circumstances: Contralateral Axillary Mets

- BC involvement of the **contralateral axilla** meets staging criteria for **distant spread** but may be **more representative of regional disease**
- Aberrant lymphatic drainage to the contralateral axilla is **relatively common** after primary breast surgery, particularly in patients who have undergone **ALND**
- Patients with **isolated contralateral axillary recurrence** have **better outcomes** compared to patients with distant metastases
- Systematic review: **OS: 82.6%** and **DFS: 65.2%** (mean F/U: 50.3 mos)
- Given these more favorable outcomes than MBC, **definitive management with ALND followed by systemic therapy and radiotherapy** should be considered

Summary I

- **Recent advances in systemic therapy have resulted in significant improvements in survival for patients with MBC**
- **Surgery to the primary tumor in patients with de novo MBC does not confer any advantage over systemic therapy**
- **However, there may be some benefit in women with controlled systemic disease who are hormone receptor positive with bone-predominant metastases**
- **Due to lack of randomized trials and heterogeneous disease biology, treatment decisions for patients with OMBC vary widely**

Summary II

- **New systemic therapies (targeted therapies and immunotherapy) have improved outcomes in patients with MBC**
- **Metastases-directed therapies for patients with limited metastatic disease have become more relevant**
- **SBRT has gained popularity in the setting of OMBC due to its excellent efficacy and lower rates of associated toxicity**
- **Results of a randomized phase II trial (NRG BR002) did not show improvement in PFS and OS with SBRT in patients with OMBC**
- **A remaining significant challenge is patient selection for SBRT and improvement in the understanding of the distinct biology of OMBC**

Thank You!