# A Prospective Analysis of Surgery and Survival in Stage IV Breast Cancer (TBCRC 013)

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Translational Breast Cancer Research Consortium

PRESENTED AT: ASCO ANNUAL MEETING '16



Presented By Tari King at 2016 ASCO Annual Meeting

# Background

- The role of surgery for the primary tumor in *de novo* Stage IV breast cancer remains controversial

- Retrospective data suggests a consistent survival benefit: HR 0.69 (0.63-0.77), p <0.00001
  - most evident in the setting of multimodality care
  - most evident in populations with fewer ER+ cancers

- Limited prospective data do not support a survival benefit

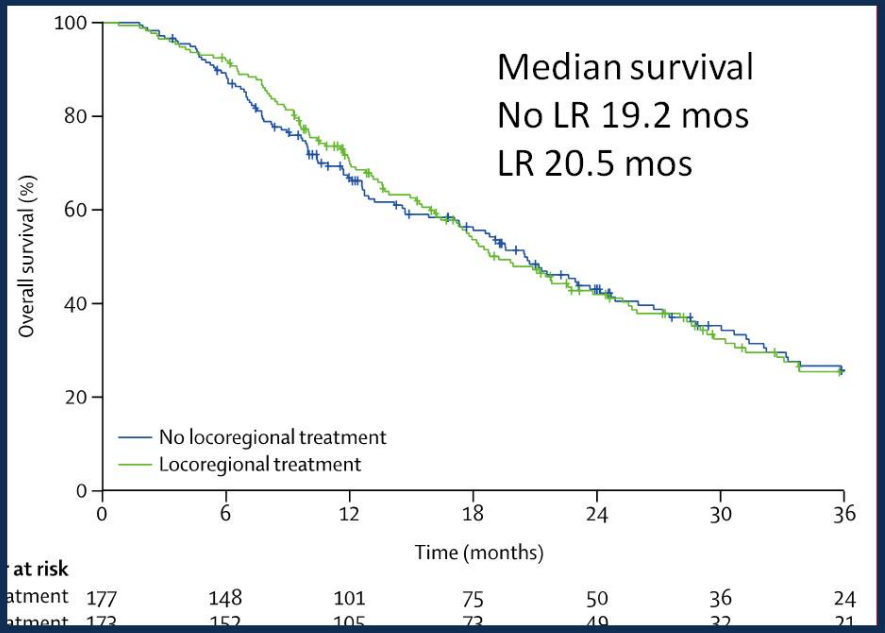
Petrelli et al. Med Oncol 2012;29:3282-3290

# Prospective Randomized Trials Examining the Role of Local-Regional Treatment in Stage IV disease

| Study | Accrual Period | Accrual Goal | Systemic Treatment Before Randomization | Status |
|---|---|---|---|---|
| India | 2005-12 | 350 | Yes | *Closed* |
| Turkey | 2008-12 | 271 | No | *Closed* |
| Danish | 2011-16 | 516 | No | *Closed* |
| USA, Canada | 2011-15 | 368 | Yes | *Closed* |
| Japan | 2011-16 | 500 | Yes | Open |
| Austria | 2010-19 | 254 | No → Yes | Open |

# Background: Surgery and Survival

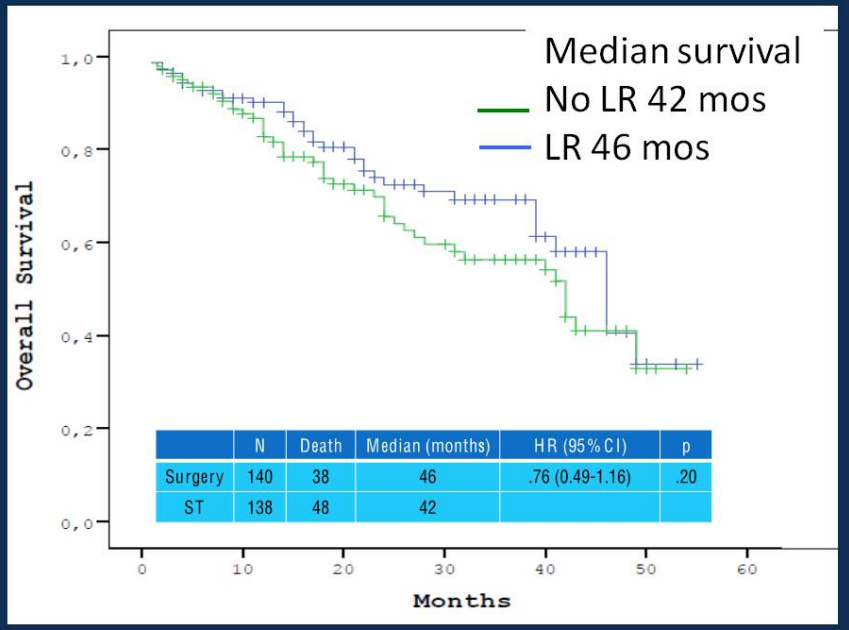
India, Tata Memorial Hospital
surgery after response to tx




Median patient age 47yrs
60% ER positive; 30% Her2+
1 pt anti-Her2 therapy
Median f/u 23 mos (12.2-38.7)

Badwe et al. Lancet Oncology 2015

Turkish Study, MF07-01
surgery before systemic tx




Median patient age >50 yrs
80% ER positive, 30% Her2+
targeted therapy
Median f/u 17-18 mos

Soran et al. 2013 SABC Symposium

# TBCRC 013: Prospective Registry

- Characterize patients presenting with stage IV breast cancer in the modern era
  - Response to first-line therapy
  - Proportion of patients who undergo surgery of the primary tumor
  - Surgical decision-making process*
- Correlate molecular characteristics of the primary tumor with conventional prognostic factors, surgery and survival
- Determine the incidence of uncontrolled local disease and the frequency with which surgical palliation is needed
- Perform correlative molecular studies

*Presented ASBrS 2016

# TBCRC 013

- **Eligibility**
  - *de novo* Stage IV breast cancer with an intact primary tumor
  - metastatic disease identified within 3 months of primary surgery
  - tissue from primary tumor and metastatic lesion
- **Accrual July 2009 – April 2012**
  - 127 eligible patients, 14 institutions, two cohorts
  - cohort A: intact primary tumor (n=112)
  - cohort B: metastases within 3 months of primary surgery (n=15)
- **Correlative Science**
  - Fackler MJ et al. Novel methylated biomarkers and a robust assay to detect circulating tumor DNA in metastatic breast cancer. *Cancer Res 2014*
  - King T et al. Prognostic Impact of 21-Gene Recurrence Score in Patients with Stage IV Breast cancer: TBCRC013. *JCO 2016*

# TBCRC 013: Cohort A Outcomes

- 112pts with de novo Stage IV disease and an intact primary tumor
- 1st line systemic therapy per treating physician
- Responders to 1st line therapy (stable, partial, or complete response of distant disease per treating physician) offered opportunity to discuss elective surgery
- Elective surgery - surgery performed in the absence of local symptoms or the need for local control
- Patient and tumor characteristics, response to systemic therapy and surgery of the primary tumor were correlated with 3yr OS using log rank, Kaplan Meier and Cox regression

# TBCRC 013 Cohort A
# Patient Characteristics

Median Patient Age:
51 yrs (21-77yrs)

Median Tumor Size:
3.2cm (0.8-15cm)

ECOG score
0: 56 (50%)
1: 51 (46%)
>1: 5 (4%)

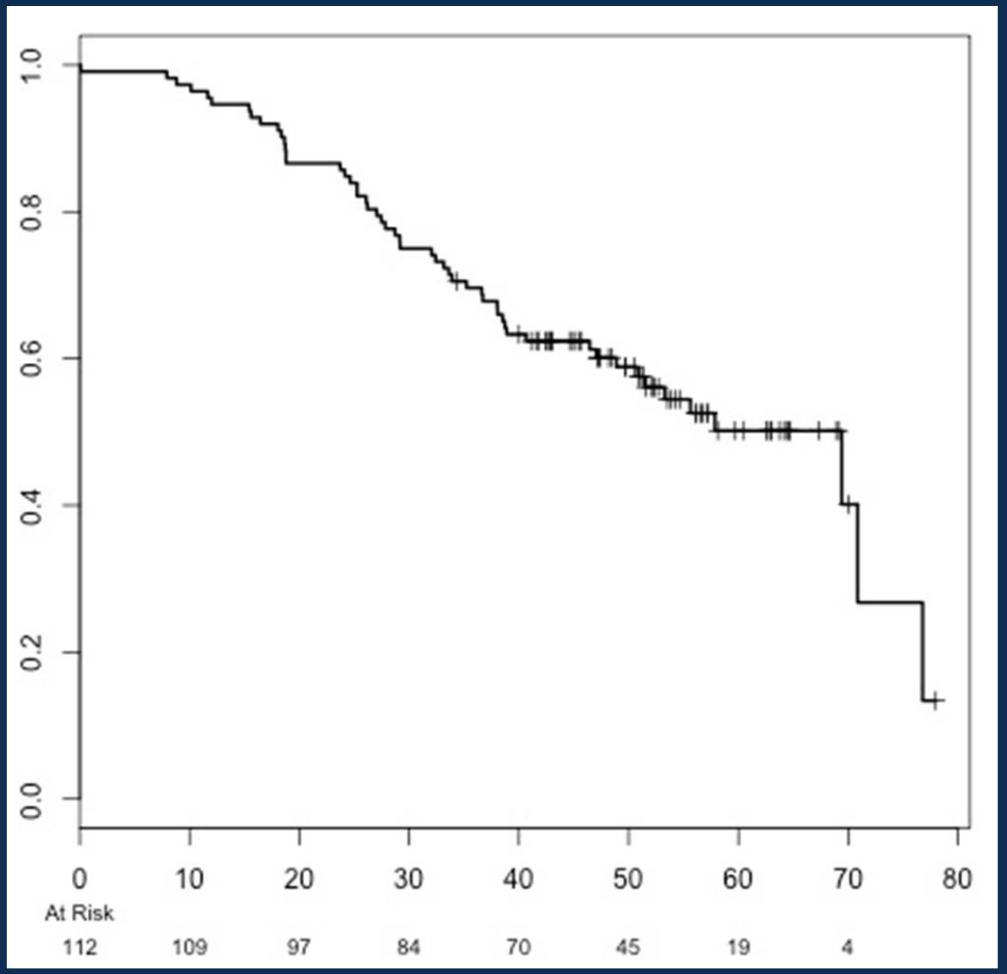
| Tumor Subtype | |
|---|---|
| **HR+HER2-** | **71 (63%)** |
| **HR+HER2+** | **24 (21%)** |
| HR-HER2+ | 9 (8%) |
| Triple Negative | 8 (7%) |
| **Site of Mets at dx** | |
| **Bone Only** | **51 (46%)** |
| Visceral Only | 26 (23%) |
| Both | 27 (24%) |
| Other | 8 (7%) |
| **# Met Sites at dx** | |
| **Single Organ** | **64 (57%)** |
| >1 Organ | 48 (43%) |

# TBCRC 013 Cohort A
# First Line Treatment

| | N=112 |
|---|---|
| **Chemotherapy alone** | **27 (24%)** |
| **Endocrine therapy alone** | **52 (46%)** |
| Chemotherapy + Endocrine therapy | 5 (4%) |
| **Chemotherapy + Trastuzumab** | **19 (17%)** |
| Endocrine therapy + Trastuzumab | 6 (5%) |
| Other** | 3 (3%) |

**trastuzumab only (1), Endocrine, chemotherapy and trastuzumab (2)

# TBCRC 013 Cohort A
# Overall Survival




N=112

3yrs OS 70%
(95%CI 63-79%)

Median Survival
69 mos (51 – NR)

Median follow-up 54 mos
(34-78mos)

# TBCRC 013 Cohort A

# Response to 1st line therapy

*1 lost to f/u

**N=112***

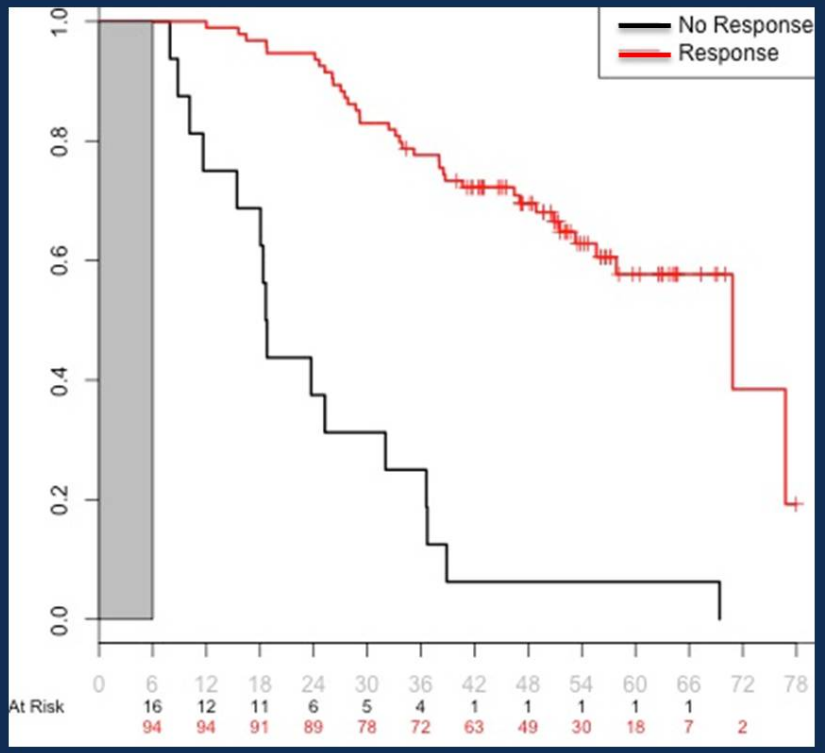
**94 (85%)**
**Responders (R)**

**17 (15%)**
**Non-Responders (NR)**

- ER + was the only baseline difference between Responders (88%) and Non-Responders (65%), p=0.02

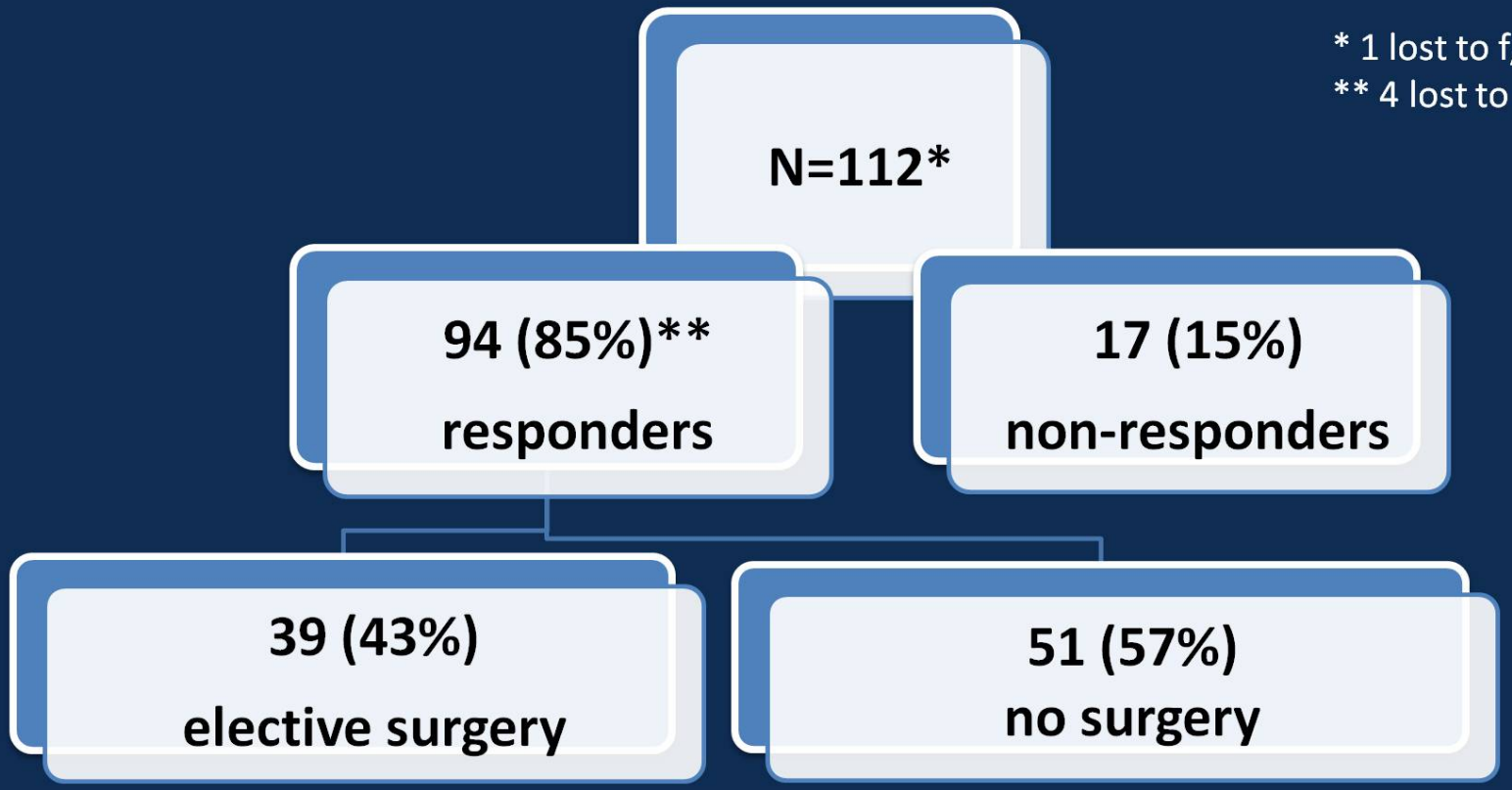
# Survival: Responders vs Non-Responders Landmark analysis at 6 months

*6 mos, surrogate for time to response assessment after 1st line therapy, per treating physician*




| | N | median survival, mos | 30 mo survival (95%CI) | P |
|---|---|---|---|---|
| R | 90 | 65 mos (52-NR) | 78% (70-87) | < 0.001 |
| NR | 16 | 13 mos (9-31) | 24% (10-55) | |

# TBCRC 013: Surgical Uptake




* 1 lost to f/u
** 4 lost to f/u

Median time to elective surgery 7 mos (3-20mos)

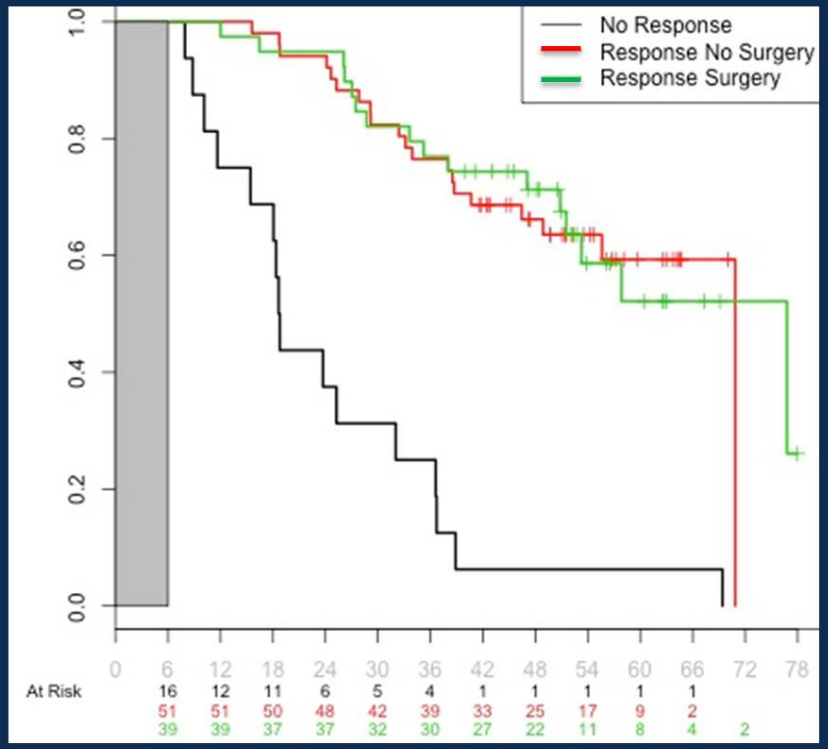
# TBCRC 013 Cohort A
# Characteristics by Surgery

| | Surgery N=39 | No Surgery N=51 | p |
|---|---|---|---|
| Median Age | 49yrs (21-73) | 52yrs (29-74) | 0.17 |
| **Tumor Size** | **3.8cm (1.6-12)** | **3.2cm (0.8-15)** | **0.01** |
| Tumor Subtype (ER+ vs other) | 34 (87%) | 46 (90%) | 0.26 |
| Site of Mets at Dx (bone vs other) | 19 (49%) | 22 (43%) | 0.45 |
| **Single Organ Metastatic Disease** | **30 (77%)** | **21 (41%)** | **0.001** |
| **1st line chemotherapy** | **15 (39%)** | **9 (17%)** | **0.002** |

- Race, marital status, employment status, income level, education and co-morbidities did not differ by use of surgery

# Multivariate Analysis: Survival

Stepwise Cox regression: including age, size, ECOG, HR, Her2, tumor grade, response and surgery




| | N | Median Survival, mos | 30 mos survival (95%CI) |
|---|---|---|---|
| Non-Responders | 16 | 13 mos (9-31) | 24% (10-55) |
| Responders, No Surgery (red) | 51 | 65 mos (50-NR) | 76% (66-89) |
| Responders, Surgery (green) | 39 | 71 mos (46-NR) | 77% (65-91) |

TBCRC 013 Cohort A

# Survival by ER / HER2 and Surgery

| Responders | Surgery | N | Median Survival, mos | 3yrOS (95%CI) | p |
|---|---|---|---|---|---|
| All | N | 51 | 71 mos(56-NR) | 76% (66-89) | 0.85 |
| | Y | 39 | 77 mos (52-NR) | 77%(65-91) | |
| | | | | | |
| ER+ | N | 46 | 71 mos (56-NR) | 78% (67-91) | 0.47 |
| | Y | 34 | 77 mos (53-NR) | 79% (67-94) | |
| | | | | | |
| HER2+ | N | 12 | NR (NR-NR) | 83% (65-100) | 0.39 |
| | Y | 15 | 77 mos (77-NR) | 100% (100-100) | |

TBCRC 013 Cohort A

# Survival by ER / HER2 and Surgery

| Responders | Surgery | N | Median Survival, mos | 3yrOS (95%CI) | p |
|---|---|---|---|---|---|
| ER+HER2+ | N | 8 | NR (NR-NR) | 88% (67-100) | 0.07 |
| | Y | 12 | 77 mos (77-NR) | 100% (100-100) | |
| | | | | | |
| ER+HER2- | N | 38 | 71 mos (49-NR) | 76% (64-91) | 0.37 |
| | Y | 22 | 53 mos (51-NR) | 68% (51-91) | |
| | | | | | |
| ER-HER2+ | N | 4 | NR (24-NR) | 75% (43-100) | 0.51 |
| | Y | 3 | 47 mos (38-NR) | 100% (100-100) | |

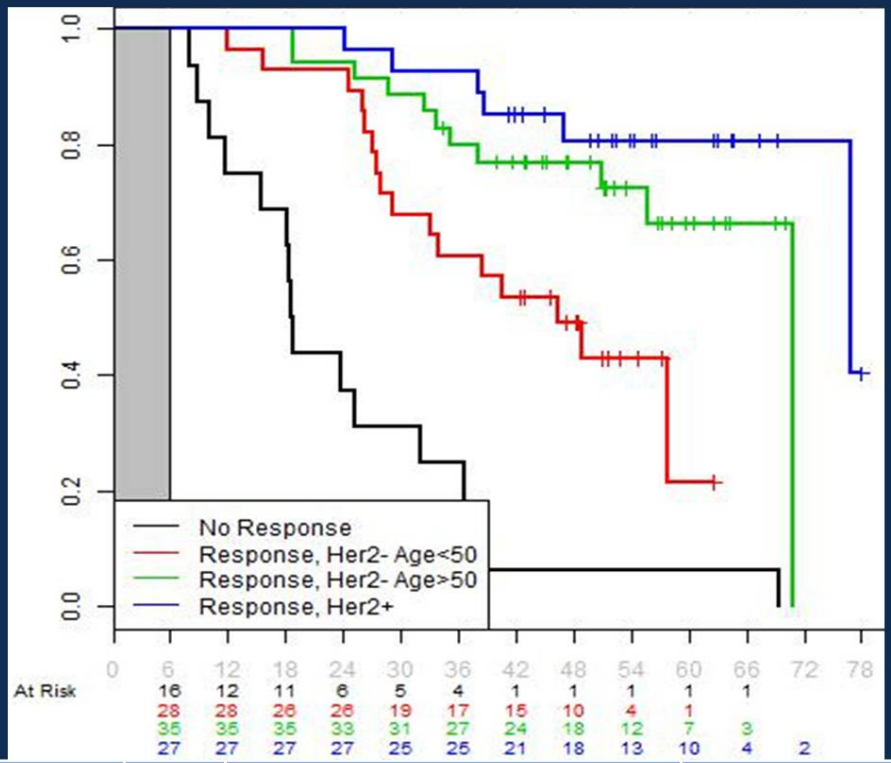
ER-HER2- N= 3 responders, too few for analysis by surgery

# Multivariate Analysis: Survival

Recursive partitioning with ten-fold cross validation

Variables: age*, size, ECOG, HR, Her2, response and surgery

**grade and age, strongly inversely correlated*




| | N | Median survival, mos | 30 mo survival (95%CI) |
|---|---|---|---|
| Non-Responders (black) | 16 | 13 mos (13-31) | 25% (11-55) |
| Response, HER2-, age <50 (red) | 16 | 40 mos (40-NR) | 61% (45-80) |
| Response, HER2-, age>50 (green) | 11 | 65 mos (65-NR) | 80% (68-93) |
| Response, HER2+ (blue) | 6 | 71 mos (17-NR) | 93% (83-100) |

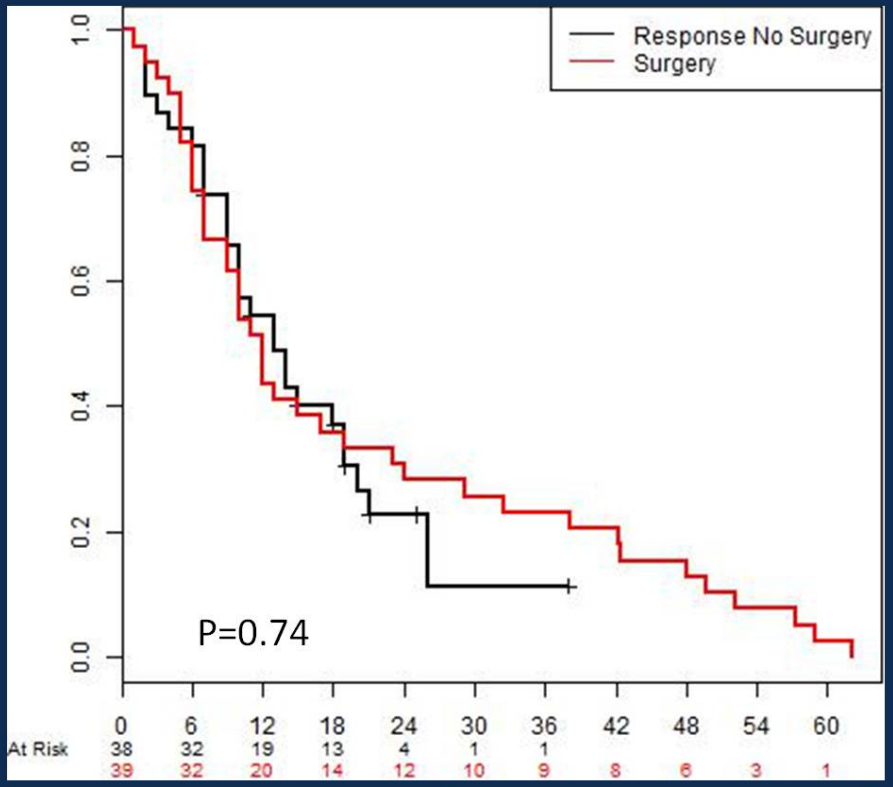
# TBCRC 013: Exploratory Analysis

- 21 gene recurrence score, ER+ HER2- patients

| | Surgery | N | Median Survival, mos | 3yrOS (95%CI) | p |
|---|---|---|---|---|---|
| Low Risk RS <18 | N | 16 | NR (39-NR) | 75% (57-99) | 0.96 |
| | Y | 5 | NR (29-NR) | 67% (30-100) | |
| | | | | | |
| Intermediate RS 18-30 | N | 9 | 71 (0-NR) | 89% (71-100) | 0.31 |
| | Y | 12 | 52 (52-NR) | 80% (52-100) | |
| | | | | | |
| High Risk RS >=31 | N | 13 | 32 (19-NR) | 39% (19-77) | 0.33 |
| | Y | 5 | 26 (26-NR) | 40% (14-100) | |

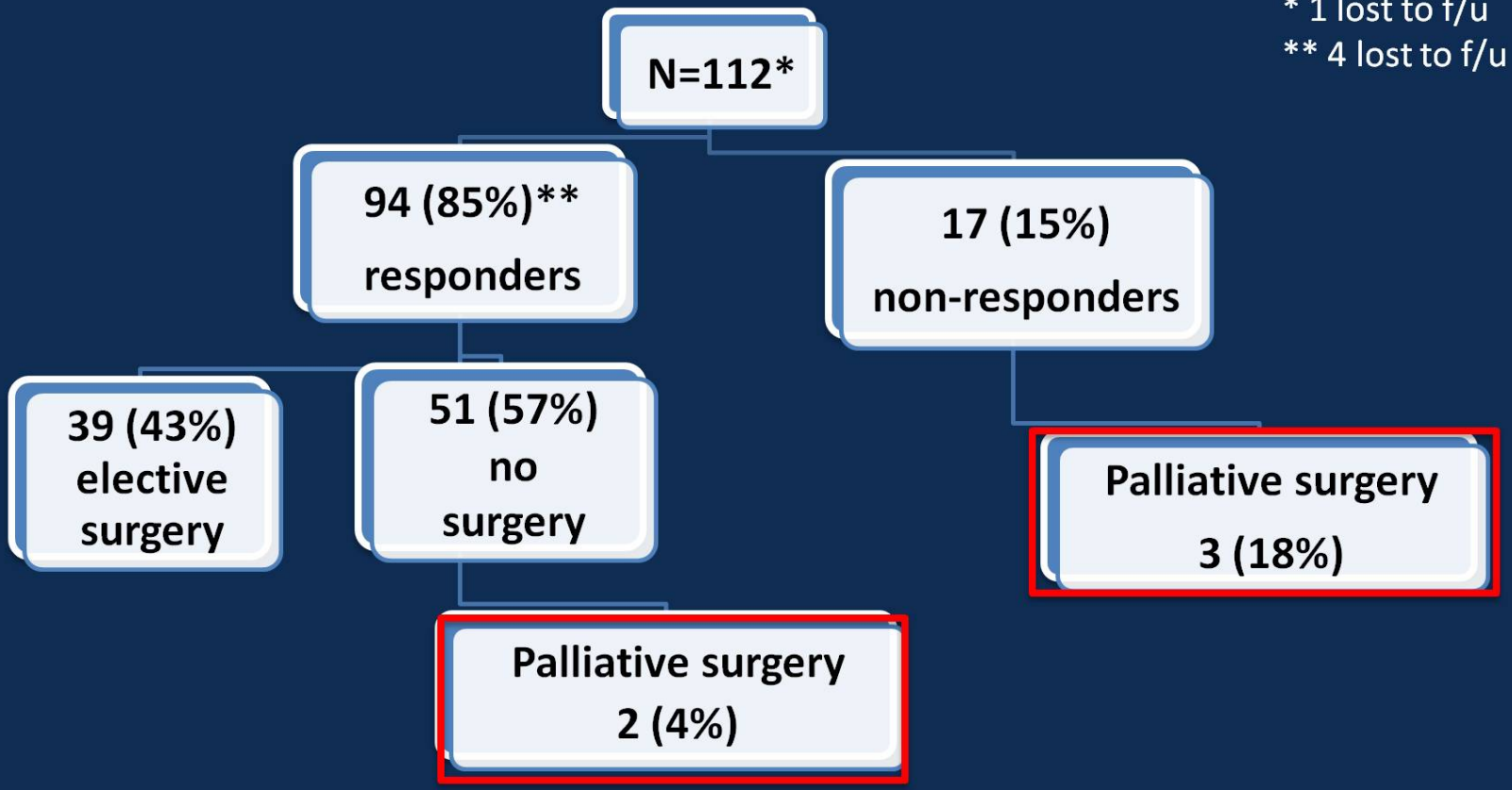
# TBCRC 013: Progression Free Survival

Only includes responders who remained progression free at 6 months – all *theoretically* eligible for surgery




| | Median TTP mos |
|---|---|
| No surgery (n=38) | 13 mos (10-20) |
| Surgery (n=39) | 12 mos (9-23) |

# TBCRC 013: Palliative Surgery




Median time to palliative surgery 17 mos (8-35 mos)

# TBCRC 013: Conclusions

- In this prospective registry study, 3yr overall survival among patients presenting with de novo stage IV disease is 70%
- The majority of patients (85%) responded to 1st line therapy and response was significantly associated with survival
- Among patients who respond to systemic therapy
  - the need for palliative surgery is uncommon
  - progression free survival is not negatively impacted by surgery

# TBCRC 013: Conclusions

- Patients selected for surgery more likely to have single organ metastatic disease and to receive 1st line chemotherapy
- Surgery did not impact survival irrespective of tumor subtype
- HER2 status and patient age remain strong prognostic factors
  - Further investigation is needed to determine if subsets of patients will benefit from surgery
- Elective surgery for the primary tumor should not be considered outside of a clinical trial

# Special Thanks to …

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The Breast Cancer Research Foundation®

Susan G. Komen For The Cure

# … for their support of the TBCRC

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