

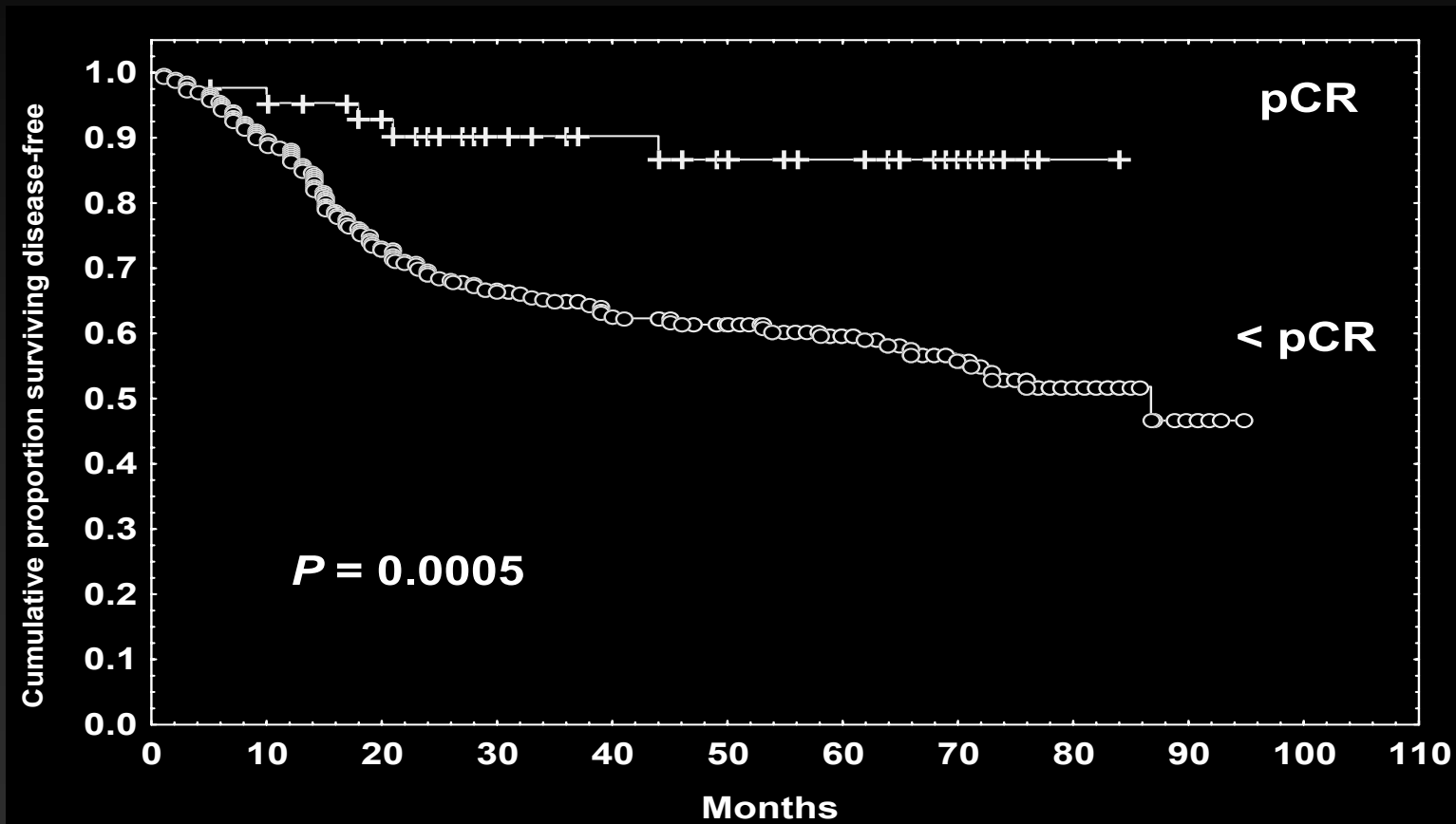
Preoperative Therapy in Breast Cancer: Current Status and Future Prospectives

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Who benefits from a particular adjuvant chemotherapy?



Those who have a complete eradication of their breast cancer (pCR) by preoperative chemotherapy benefit !

Kuerer H et al. J Clin Oncol 1999

Herceptin[®] as single-agent PST: phase II trial results

- **Pilot study in patients (n=11) with HER2-positive breast cancer**
- **Patients received single-agent Herceptin[®] as PST**
 - **4mg/kg, followed by 2mg/kg**
- **Herceptin[®] showed clinical efficacy and was well tolerated**
 - **one pCR**
 - **four partial remissions**
 - **six minor responses**

Phase II Trials of Trastuzumab Neoadjuvant Therapy for Breast Cancer

| Study (N) | Regimen | Percent | | |
|---------------------|-------------------------|---------|-----|-----|
| | | ORR | cCR | pCR |
| Mohsin 2005 | T qw × 3, T + D qw × 12 | – | – | – |
| Gennari 2004 (11) | T qw × 4 | 36 | 0 | 9 |
| Burstein 2003 (40) | T qw × 12 + P qw × 4 | 75 | 30 | 18 |
| Bines 2003 (33) | T qw × 12 + D q3w × 4 | 70 | 24 | 12 |
| Harris 2003 (42) | T qw × 12 + V qw × 12 | 88 | 38 | 19 |
| Limentani 2003 (45) | T qw × 12 + DV q2w × 6 | 100 | 59 | 31* |

*42% of patients had <5 mm residual tumors.

Mohsin et al. *J Clin Oncol.* 2005;23:epub ahead of print; Gennari et al. *Clin Cancer Res.* 2004;10:5650; Burstein et al. *J Clin Oncol.* 2003;21:46; Bines et al. *Breast Cancer Res Treat.* 2003;82:S56. Abstract 243; Harris et al. *Proc Am Soc Clin Oncol.* 2003;22:22. Abstract 86; Limentani et al. *Breast Cancer Res Treat.* 2003;83:S58. Abstract 251.

Trastuzumab and
Chemotherapy:

Together or Separately?

Why consider concurrent trastuzumab plus chemotherapy?

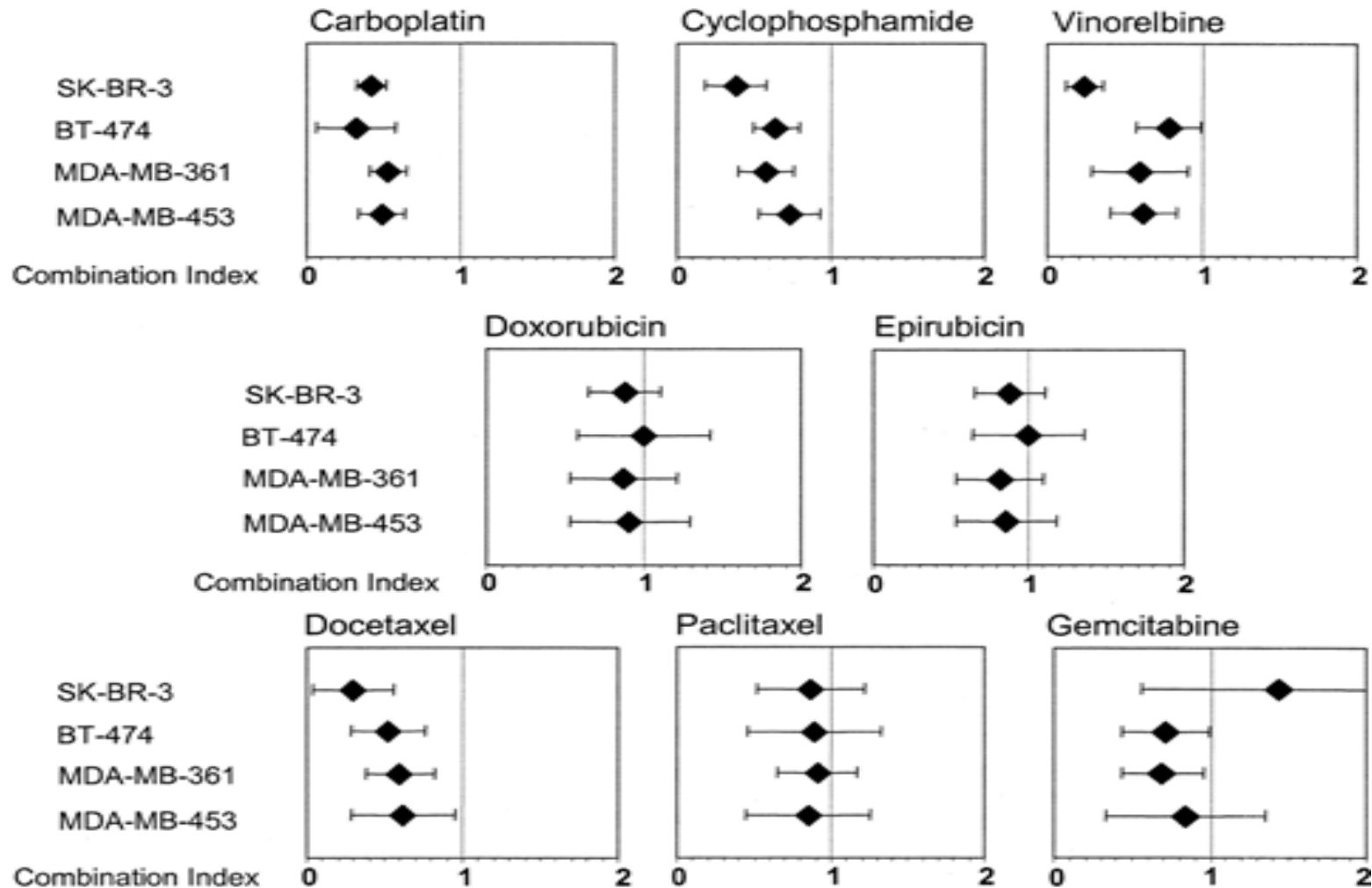
1. Better efficacy (?)
2. Shortens duration of treatment

HER2+ Advanced Breast Cancer

- Trastuzumab monotherapy
- Response rates 15 to 30%

- Trastuzumab plus chemotherapy
- Response rates 40 to 80%

Interactions between Trastuzumab and Chemotherapeutic Agents

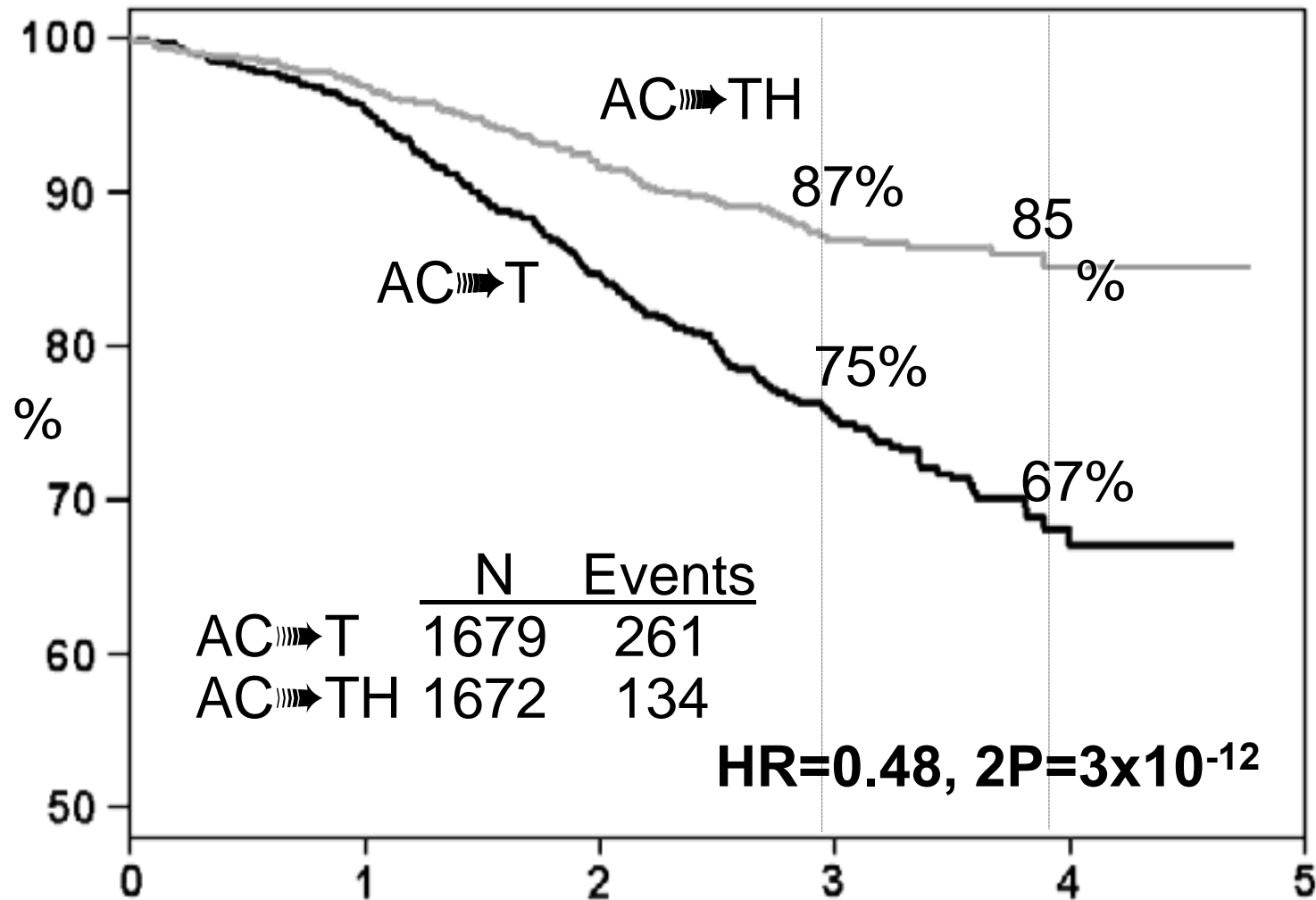


Pegram, et al. JNCI 2004

Summary of Adjuvant Trials

| | NSABP B-31 | N9831 | HERA | FinHER | BCIRG |
|--------------------|---------------|-------------|---------|---------|-------|
| HER2 testing | Central/cert | | Central | Central | FISH |
| LN+ | 93% | | 70% | 84% | 71% |
| Taxane-based chemo | 100% | | 25% | 50% | 100% |
| H schema | CON | CON vs. SEQ | SEQ | CON | CON |
| HR | 0.48 | | 0.54 | 0.42 | 0.49 |

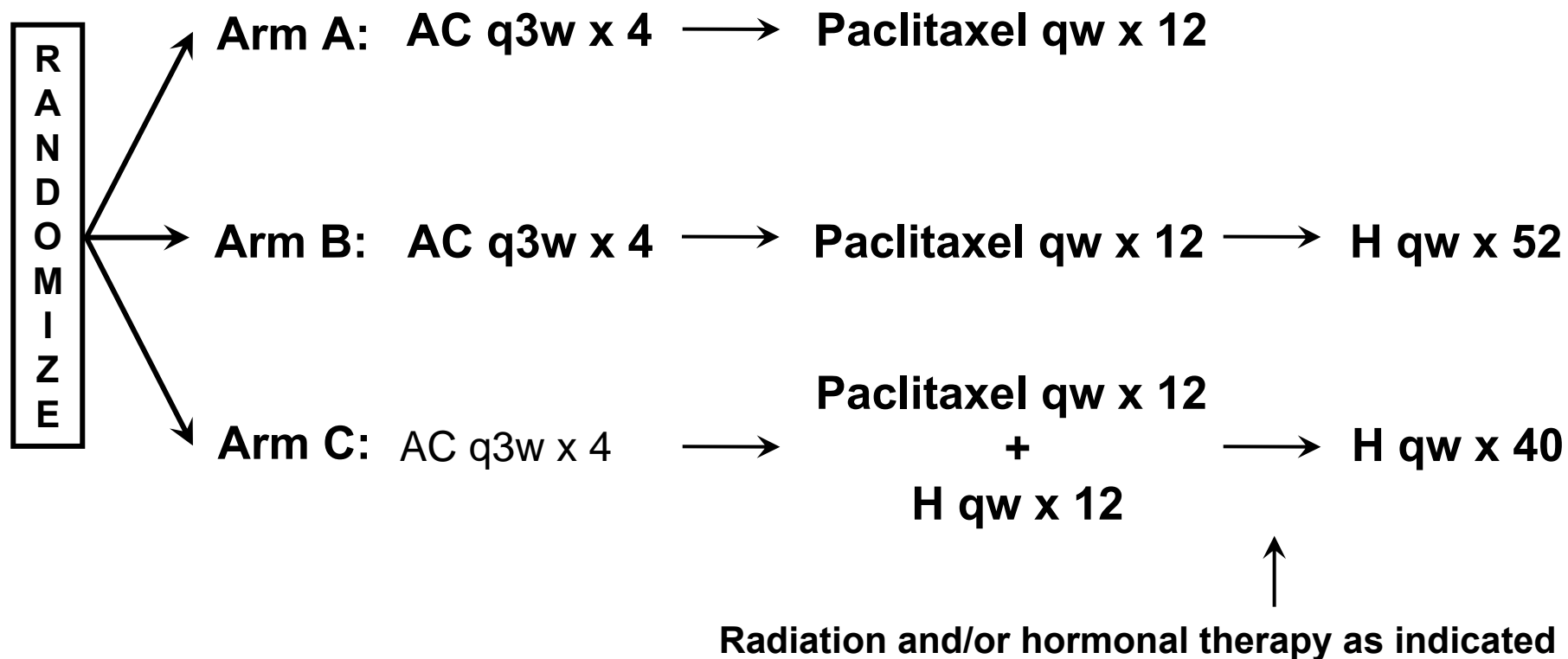
Disease-Free Survival



Years From Randomization

B31/N9831

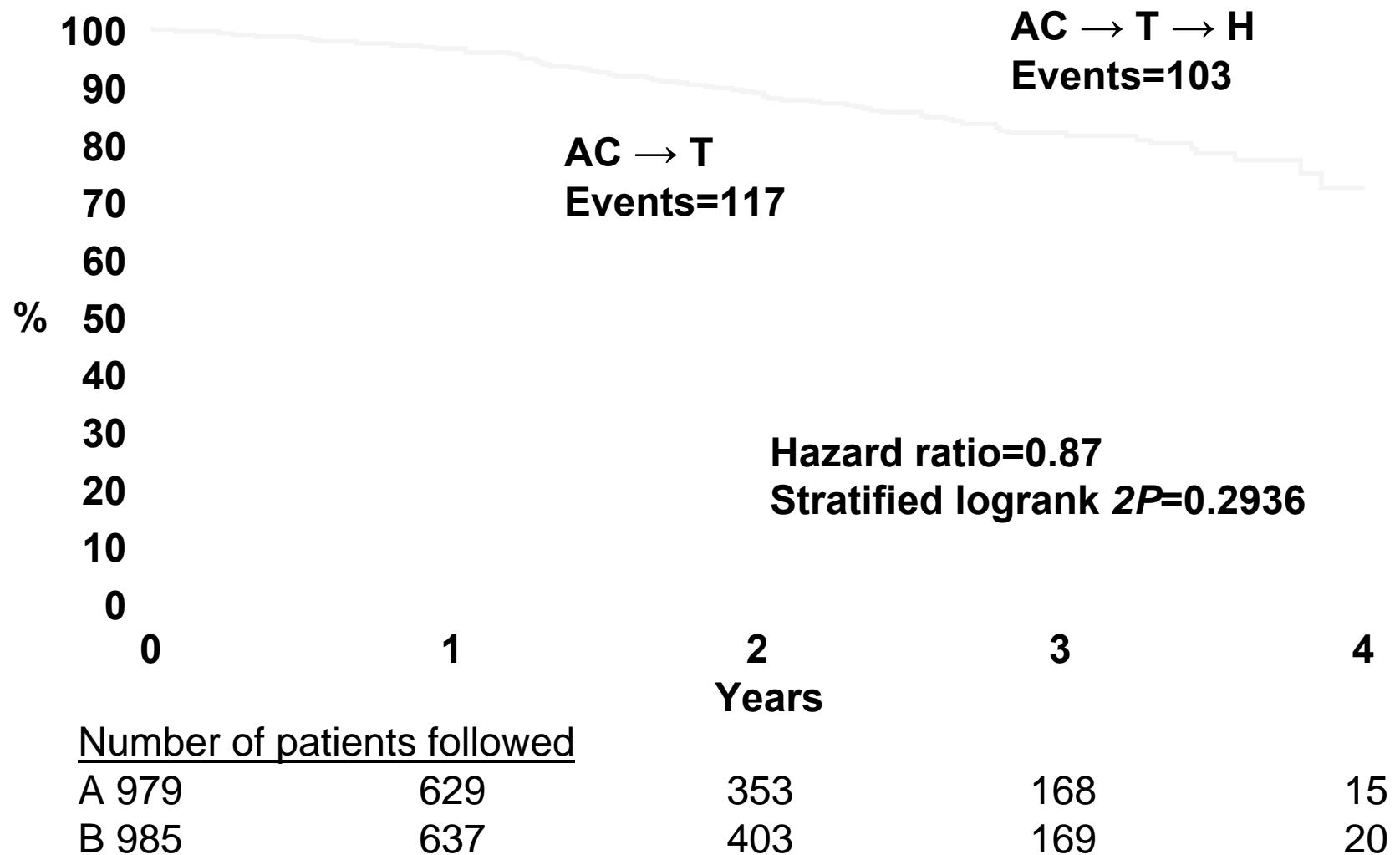
NCCTG N9831 Schema



Perez E. Protocol NCCTG-N9831. H=trastuzumab (4mg/kg loading dose, followed by 2mg/kg); doxorubicin dose 60mg/m²; cyclophosphamide, 600mg/m²; paclitaxel, 80mg/m²
q3w=every 3 weeks; qw=weekly

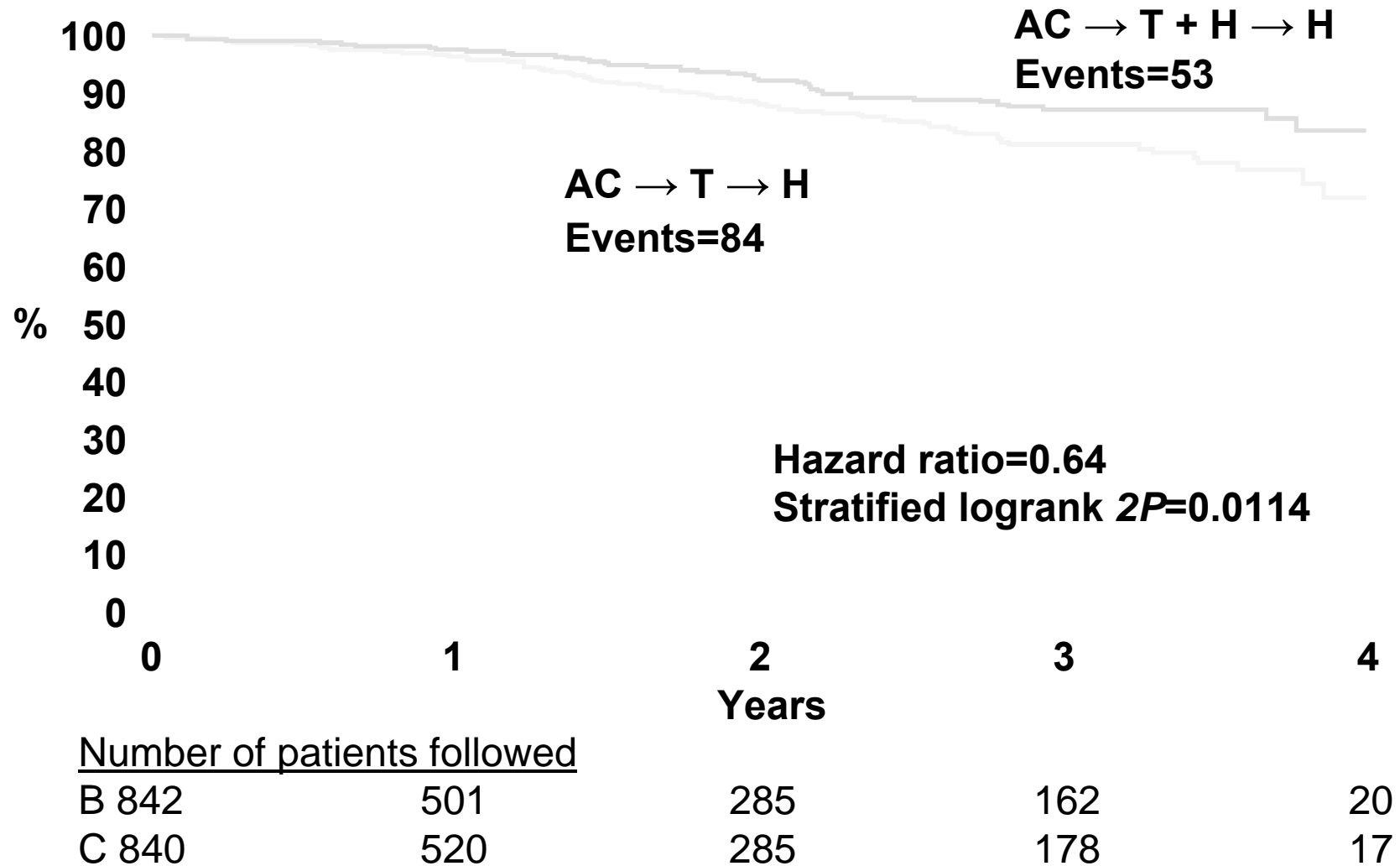
Disease-Free Survival: A vs B

N9831



Disease-Free Survival: B vs C

N9831





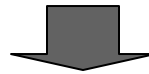
HERA TRIAL DESIGN



Women with HER2 POSITIVE invasive breast cancer IHC3+ or FISH+ centrally confirmed



Surgery + (neo)adjuvant chemotherapy (CT) ± radiotherapy



Stratification

Nodal status, adjuvant CT regimen, hormone receptor status and endocrine therapy, age, region

Randomization



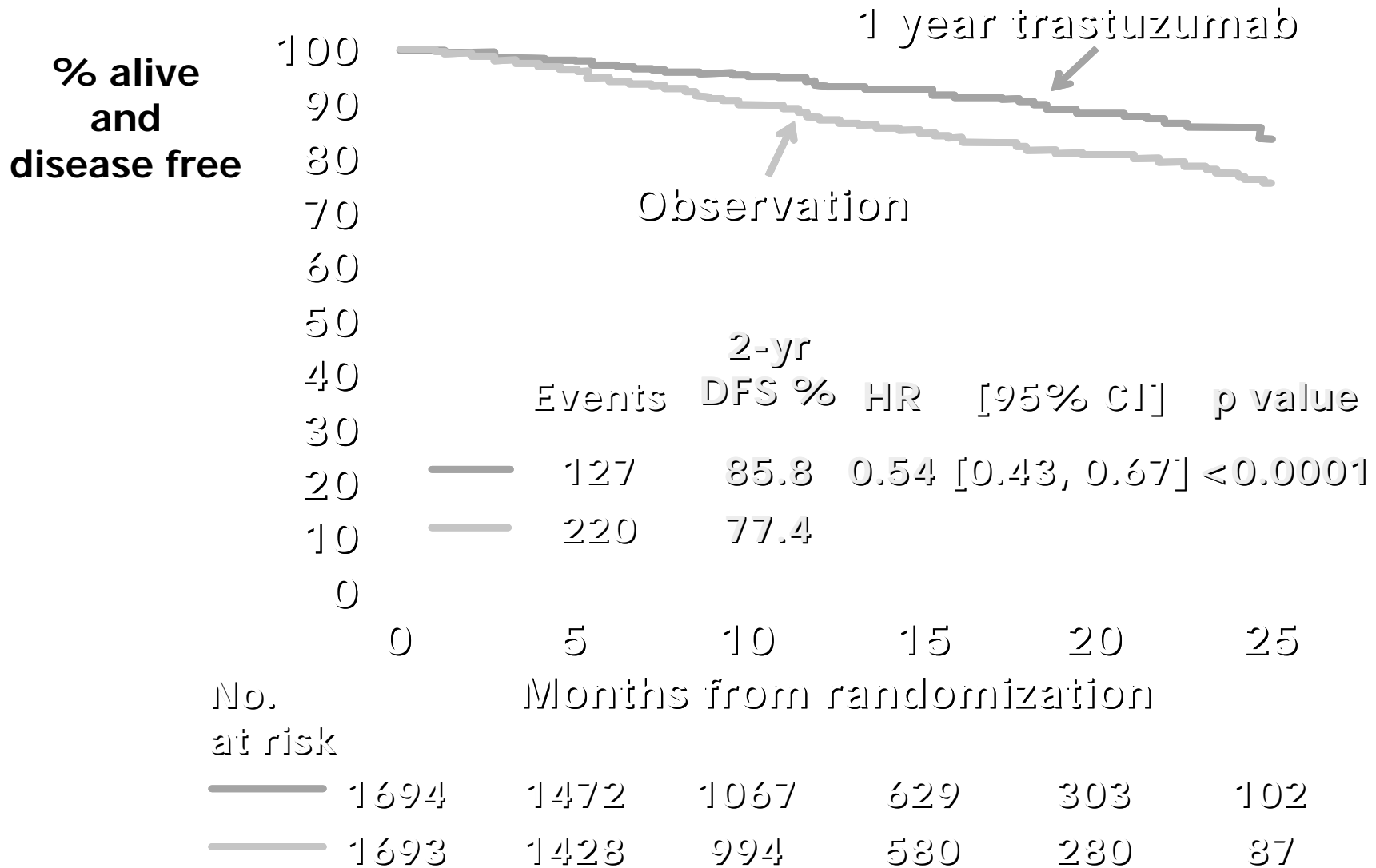
**Trastuzumab
8 mg/kg → 6 mg/kg
3 weekly x 2 years**

**Trastuzumab
8 mg/kg → 6 mg/kg
3 weekly x 1 year**

Observation



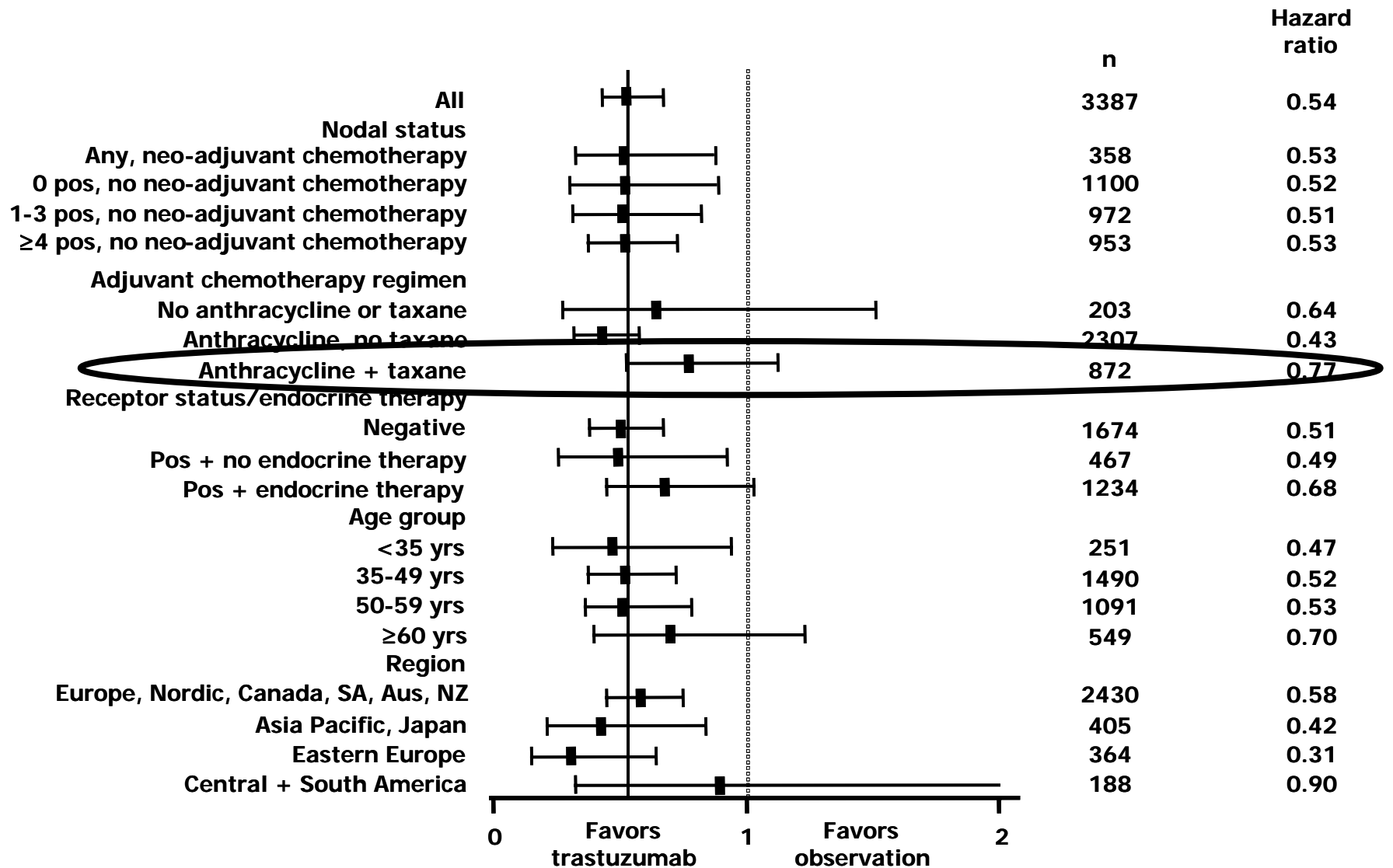
DISEASE-FREE SURVIVAL





DFS BENEFIT IN SUBGROUPS

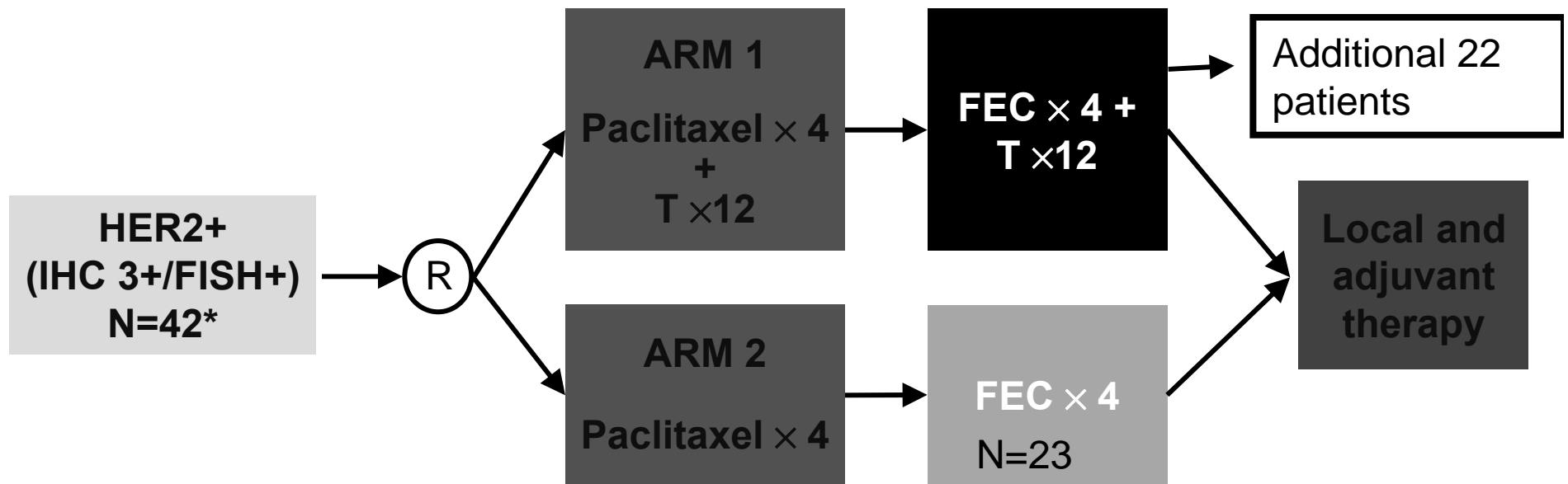
HR: 1 year trastuzumab vs observation



How can one reconcile N9831 arms A/B/C and HERA experiences?

- N9831 arms closed prematurely, thus underpowered with few events
- N9831 patients all received A- and T-based chemotherapy
- HERA subsets: least relative benefit for trastuzumab in patients also receiving A- and T-based adjuvant chemotherapy
- N9841 suggests CON > SEQ overall, and SEQ \cong NONE because of few events and “raised bar” of A- and T- chemo
- Suggests that CON > SEQ trastuzumab

Phase III Trial of Neoadjuvant Trastuzumab + Chemotherapy for Operable Breast Cancer



*Paclitaxel 225 mg/m² q3w.

FEC = 5-fluorouracil 500 mg/m² d1, 4 + epirubicin 75 mg/m² d1 + cyclophosphamide 500 mg/m² d1, all q3w.

T = trastuzumab 4 mg/kg d1, then 2 mg/kg qwx24 weeks

Buzdar et al. *J Clin Oncol.* 2005;23:3676-85

Patient Characteristics

| | Randomized Groups | | Assigned Treatment |
|---------------------------------|---------------------|-------------------|--------------------|
| | P→FEC alone N=19 | P→FEC + H N=23 | P→FEC + H N=22 |
| Age in years | | | |
| Median | 48 | 52 | 51 |
| Range | 25-75 | 29-71 | 21-70 |
| Tumor | | | |
| T1 | 2 | 2 | 3 |
| T2 | 13 | 15 | 14 |
| T3 | 4 | 5 | 5 |
| T4 | 0 | 1 | 0 |
| Nodal Status | | | |
| N0 | 7 | 10 | 9 |
| N1 | 12 | 12 | 13 |
| N2 | 0 | 1 | 0 |
| Hormonal Receptor Status | | | |
| ER + PR + | 6 | 6 | 6 |
| ER + PR - | 4 | 4 | 5 |
| ER - PR + | 1 | 3 | 1 |
| ER - PR - | 8 | 10 | 10 |

Patient Characteristics (continued)

| | Randomized Groups | | Assigned Treatment |
|---------------------|---------------------|-------------------|--------------------|
| | P→FEC alone N=19 | P→FEC + H N=23 | P→FEC + H N=22* |
| Her-2 Status | | | |
| FISH + | 17 | 20 | 4 |
| IHC 3+ only | 1 | 3 | 1 |
| IHC 3+ FISH – | 1 | 0 | 0 |
| IHC 3+ plus FISH + | | | 17 |
| Race | | | |
| White | 13 | 13 | 14 |
| African American | 3 | 1 | 3 |
| Asian | 2 | 4 | 1 |
| Hispanic | 1 | 5 | 4 |

*N= 12 patients who did not receive all therapy

2 – missed at least 1 of Day 4 5-FU

3 – missed 12 doses of Herceptin = 1 pCR

2 – missed 3 doses of Herceptin = 2 pCR

2 – missed 2 doses of Herceptin = 1 pCR

1 – missed 7 doses of Herceptin and did not receive 3 doses of taxol = 1 pCR

2 – missed 8 doses of Herceptin and did not receive 2 doses of FEC

Adverse Events

| | Randomized Groups | | Assigned Treatment |
|---|---------------------|-------------------|----------------------------------|
| | P→FEC alone N=19 | P→FEC + H N=23 | P→FEC + H N=22 |
| Neutropenia | | | |
| Grade 4 | 11 | 21 | 20 |
| Neutropenic | 8 | 8 | 6 |
| Neutropenic infections | 3 | 5 | 4 |
| Hospitalization | 1 | 3 | 5 |
| Non-Neutropenic infections | 4 | 7 | 8 |
| Chemotherapy dose reduction (due to neutropenia) | 4 | 12 | 7 |
| | | | (2 with Taxol 5 with FEC) |
| Allergic Reactions | 4 | 4 | 7 |
| (only 1 pt had dose modification. No further taxol was given after first dose) | | | |

Potential Cardiac Risk Factors by Treatment Group

| Potential Risk Factors | Randomized Groups | | Assigned Treatment |
|---------------------------------|---------------------|-------------------|--------------------|
| | P→FEC alone N=19 | P→FEC + H N=23 | P→FEC + H N=22 |
| Hypertension | 6 | 5 | 4 |
| Diabetes | 2 | 1 | 0 |
| EKG Abnormalities | 1 | 6 | 8 |
| H/O arrhythmias | 0 | 1 | 1 |
| Valvular Dysfunction | 3 | 3 | 3 |
| H/O Cerebrovascular accident | 1 | 0 | 0 |

Adverse Events (continued)

| | Randomized Groups | | Assigned Treatment |
|---|---------------------|-------------------|--------------------|
| | P→FEC alone N=19 | P→FEC + H N=23 | P→FEC + H N=22 |
| Cardiac Safety Data | | | |
| Cardiac Dysfunction | 1 (NY HC3) | 0 | 1 (NY HC1) |
| > 10% decrease in ejection fraction | 5 | 7 | 6 |
| -decrease on paclitaxel | 0 | 4 | 3 |
| -decrease on FEC | 5 | 3 | 3 |
| Of the 3 patients in the taxol regimen who had a F/U echo, 1 patient EF returned to BL. The other 2 have remained stable. The 3 patients who had a decrease after FEC has not had their follow-up evaluation yet. | 2 | 3 | |
| Abnormal Troponin-T | 0 | 1 | not evaluated |

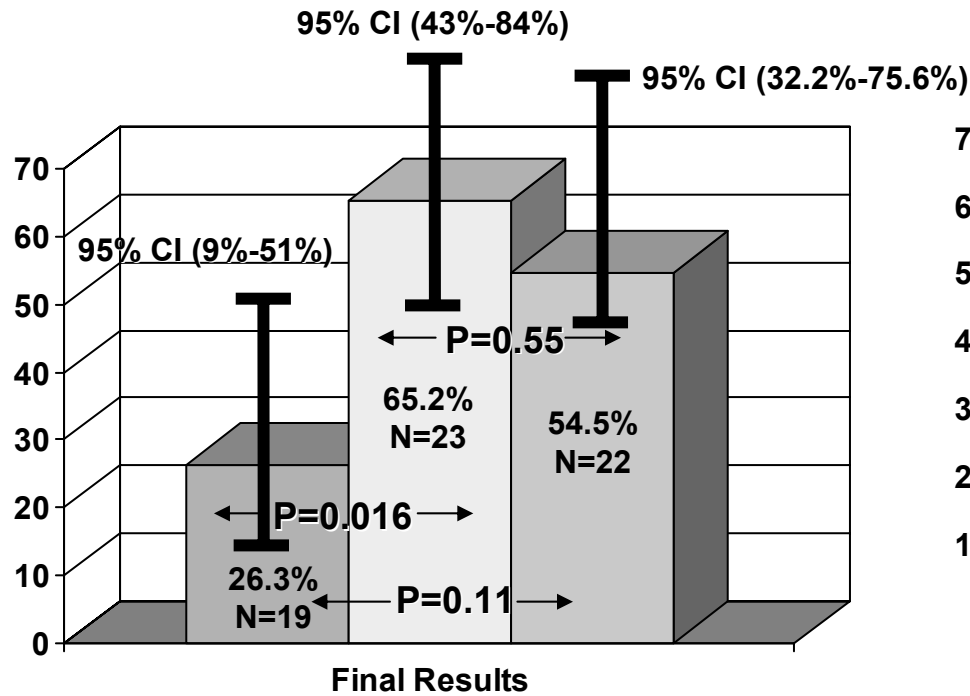
Extent of Residual Disease by Treatment

| | Randomized Groups | | Assigned Treatment |
|--|----------------------|--------------------|--------------------|
| | P→ FEC alone N=19 | P→ FEC + H N=23 | P→ FEC + H N=22 |
| Residual disease in breast | | | |
| None | 5 | 15 | 12 |
| DCIS only in CRs | 1 | 5 | 4 |
| < 1 cm | 3 | 5 | 7* |
| 1-3 cm | 9 | 1 | 3 |
| > 3 cm | 2 | 2 | 0 |
| Number of + nodes | | | |
| 0 | 15 | 20 | 20 |
| 1-3 | 2 | 3 | 2 |
| 4-10 | 2 | 0 | |
| > 10 | 0 | 0 | |
| Pathological CR by hormonal Receptor Status # of patients | | | (N=12) |
| Positive | | | 6 |
| Negative | | | 6 |
| | | | (N=22) |
| # of Segmental/Sentinel bx | | | 7 |
| # of Segmental/Axillary Dissection | | | 7 |
| # of Modified Radical/Axillary Dissection | | | 8 |

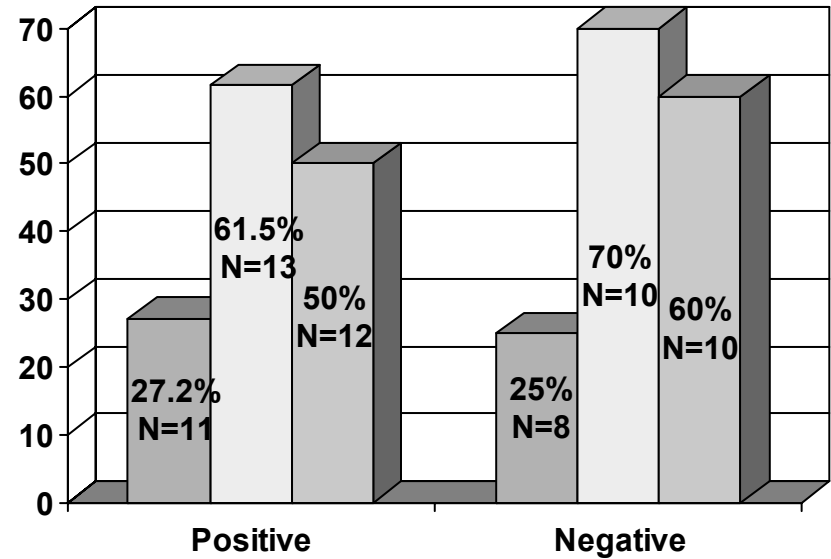
* Focal cluster of cancer cells in 5 pts

Pathological Complete Response Rates

Pathological Complete Response Rates – All patients



Pathological Complete Response Rates by Hormonal Receptor Status



 P + FEC alone

 P + FEC + H

 P + FEC + H assigned treatment

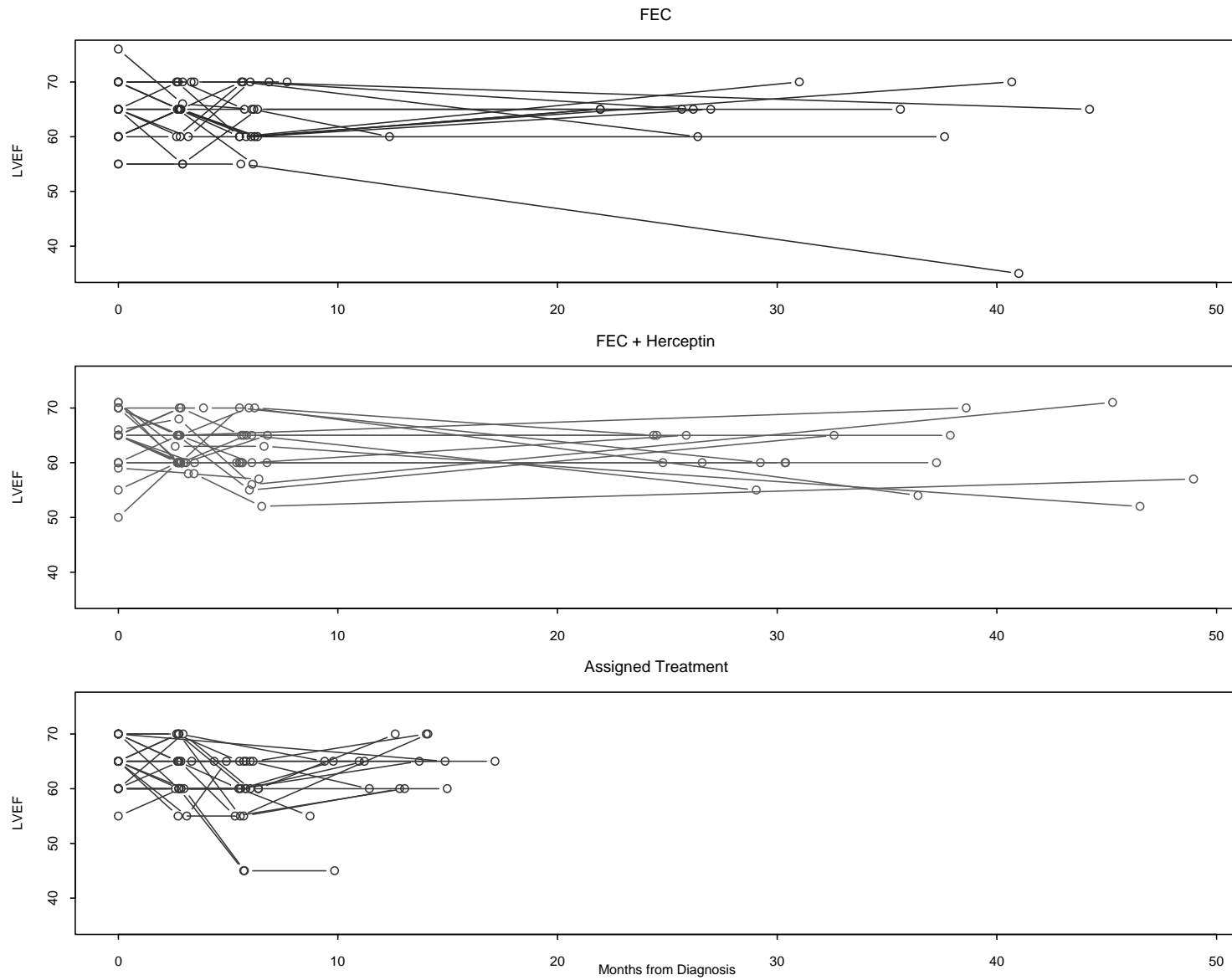
Clinical Response by Treatment

| Response | Randomized Groups | | Assigned Treatment | | | |
|---|----------------------|---------|--------------------|---------|--------------------|-----------------|
| | P→ FEC alone N=19 | Path cR | P→ FEC + H N=23 | Path cR | P→ FEC + H N=22 | Path cR N=12 |
| Clinical Evaluation | | | | | | |
| Complete response | 9 | 4 | 20 | 13 | 13 | 8 |
| Partial response | 9 | 1 | 2 | 1 | 8 | 3 |
| No change | 0 | 0 | 1 | 1 | | |
| Progressive disease | 1 | 0 | 0 | 0 | | |
| MR | | | | | 1 | 1 |
| Imaging Studies (mammogram & ultrasound) | | | | | | |
| Complete response | 5 | 4 | 12 | 7 | 7 | 5 |
| Partial response | 11 | 1 | 10 | 7 | 14 | 7 |
| No change | 2 | 0 | 1 | 1 | | |
| Progressive disease | 1 | 0 | 0 | 0 | | |
| Unknown | | | | | 1 | 0 |

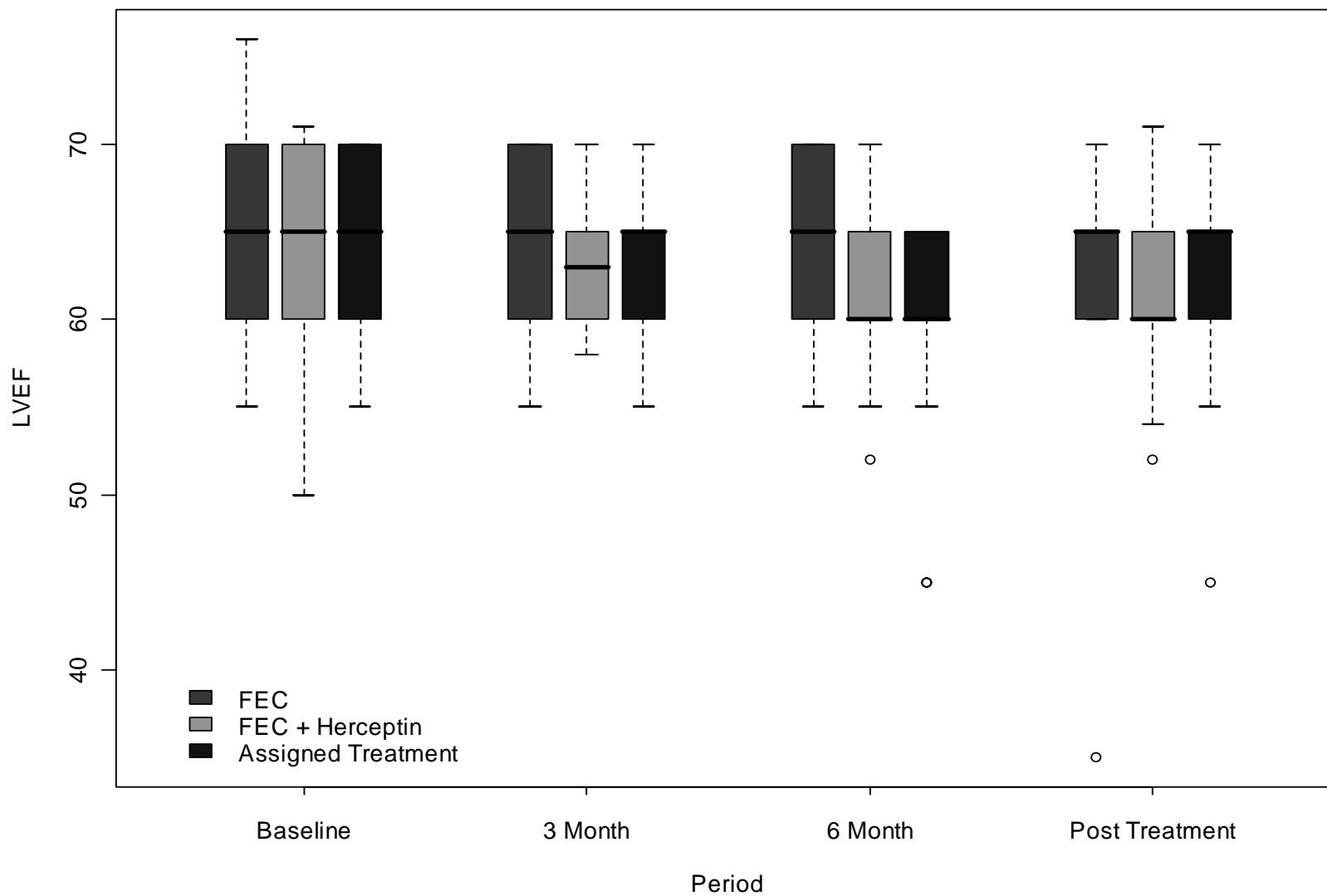
Summary of left ventricular ejection fraction (LVEF) at each assessment time

| | FEC | FEC + Herceptin | Assigned |
|-----------------------------|-----------------------|-------------------------|-----------------------|
| Baseline | | | |
| Number of patients | 19 | 23 | 22 |
| Median LVEF (range) | 65 (55-76) | 65 (50-71) | 65 (55-70) |
| 3 Month | | | |
| Number of patients | 18 | 23 | 22 |
| Months from Baseline | 2.8 (2.7-3.4) | 2.8 (0.5-7) | 2.8 (2.6-14.9) |
| Median LVEF (range) | 65 (55-70) | 63 (58-70) | 65 (55-70) |
| 6 Month | | | |
| Number of patients | 17 | 22 | 22 |
| Months from Baseline | 6 (5.5-7.7) | 5.9 (2.7-6.8) | 5.7 (4.4-9.4) |
| Median LVEF (range) | 65 (55-70) | 60 (52-70) | 60 (45-65) |
| Post Treatment | | | |
| Number of patients | 13 | 17 | 15 |
| Months from Baseline | 27 (12.4-44.2) | 30.4 (24.4 - 49) | 12.6 (6-17.7) |
| Median LVEF (range) | 65 (35-70) | 60 (52-71) | 65 (45-70) |

Ejection fraction data of individual patients by treatment - over time



Ejection data of all patients



Efficacy Update:

Median Follow-Up (months)

Initial randomized patients: 36.5 (range 26-53)

Assigned patients: 15.5 (range 12-20)

Two patients in the control group have relapsed. Of those, one patient has died.

All in Chemotherapy + trastuzumab were free of cancer.

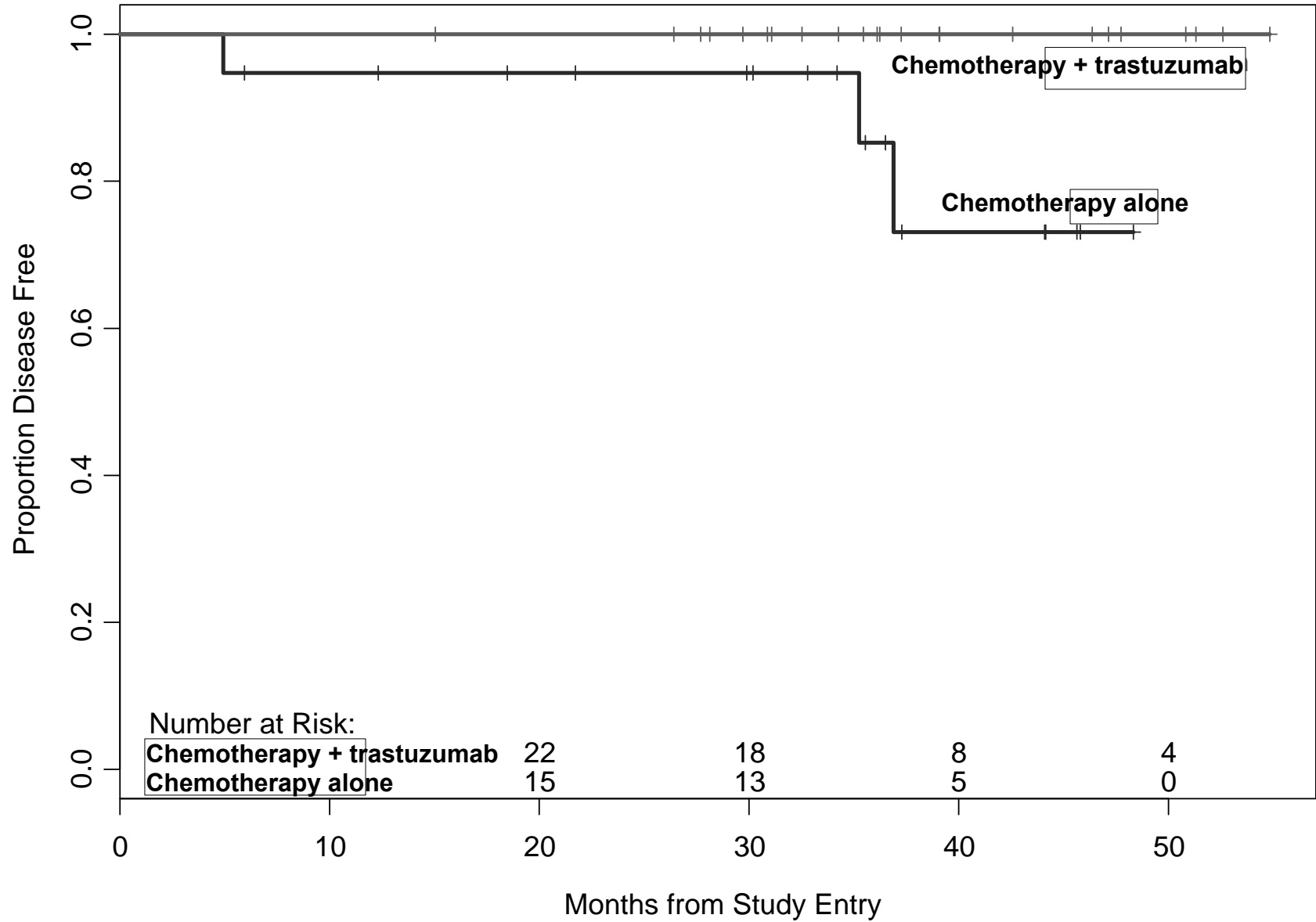
Safety Data Update:

2 patients have developed Clinical cardiac dysfunction

**One patient in control group. NY Heart association criteria = 3
Ejection fraction drop from 55 to 35%. (Prior history of
hypertension, diabetes, mitral regurgitation and had a recent
myocardial infarct)**

**One patient assigned group: NY Heart association criteria =1,
Ejection fraction decreased from 65 to 45%. (prior history of an
irregular heart rates, and had left bundle branch block)**

Disease-Free Survival of Randomized Study Population



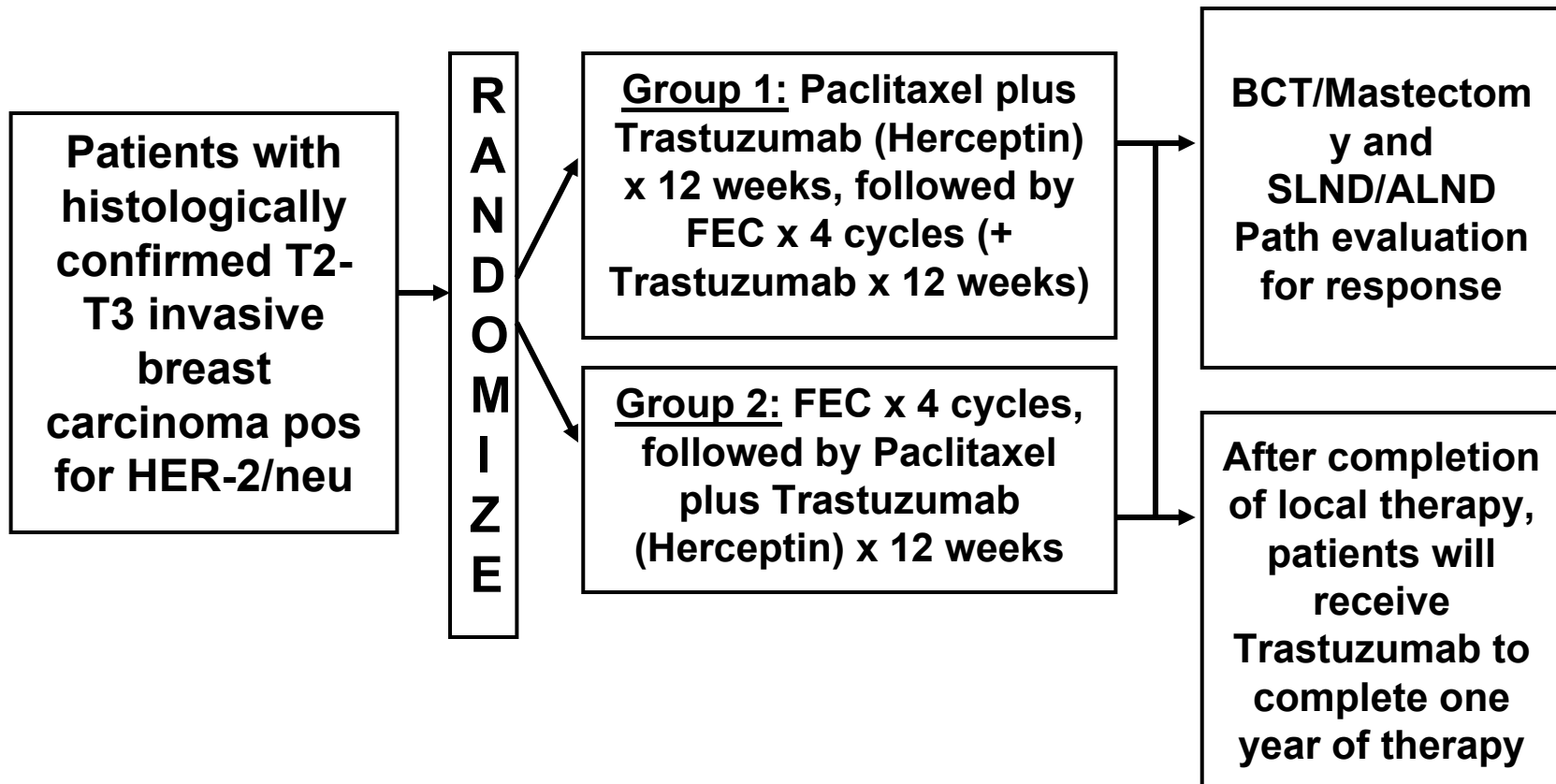
ACOSOG Z1041

A Randomized Phase III Trial Comparing a Neoadjuvant Regimen of FEC-75 Followed By Paclitaxel Plus Trastuzumab with a Neoadjuvant regimen of paclitaxel plus trastuzumab followed by FEC-75 Plus Trastuzumab in Patients with Palpable and Operable Breast Cancer

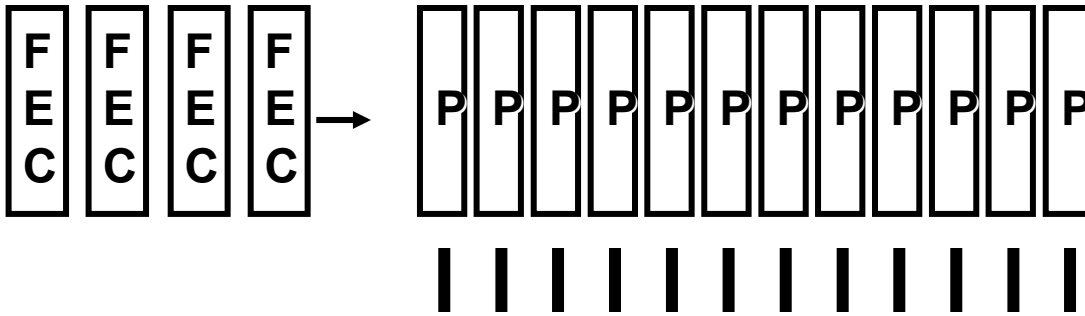
Eligibility Criteria

- **Invasive carcinoma**
- **HER2-positive using FISH or IHC at NSABP-approved lab**
- **T \geq 2.0 cm**
- **Adequate cardiac function (by MUGA scan)**
- **Adequate blood counts, hepatic and renal function**

ACOSOG Z1041

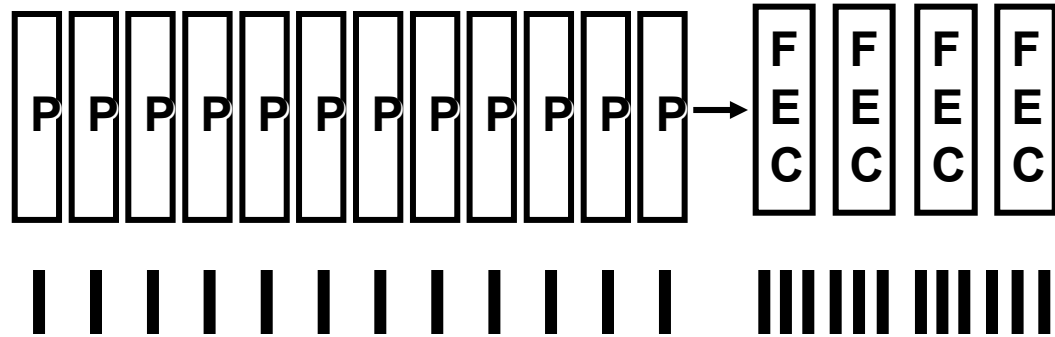


Treatment Plan



Paclitaxel (P)
80 mg/m² weekly

VS
.



- Fluorouracil 500 mg/m² IV day 1
- Epirubicin 75 mg/m² IV day 1 only
- Cyclophosphamide 500 mg/m² IV Day 1 Q 3 weeks

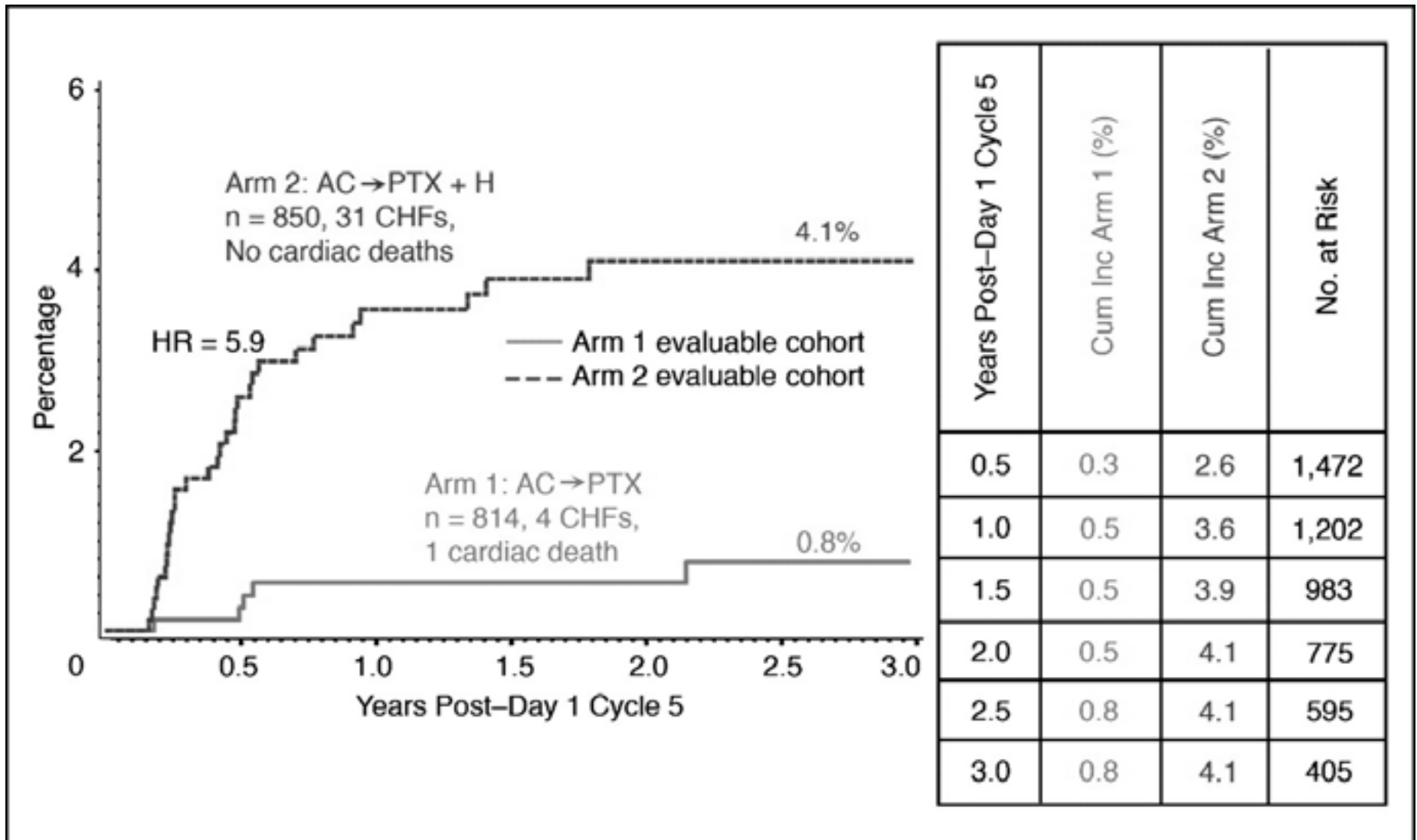
Trastuzumab (■)
4 mg/kg IV day 1,
then 2 mg/kg IV weekly

Why not consider concurrent
trastuzumab plus
chemotherapy?

Why not consider concurrent trastuzumab plus chemotherapy?

1. Greater toxicity (?)
2. Lack / loss of feasibility

Cumulative incidence of cardiac events: B-31





**Concomitant pre operative chemotherapy
and trastuzumab can achieve:**

- **high pathological complete response rates**
- **Safety data - favorable**
- **Efficacy results - very encouraging**

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Thank You !