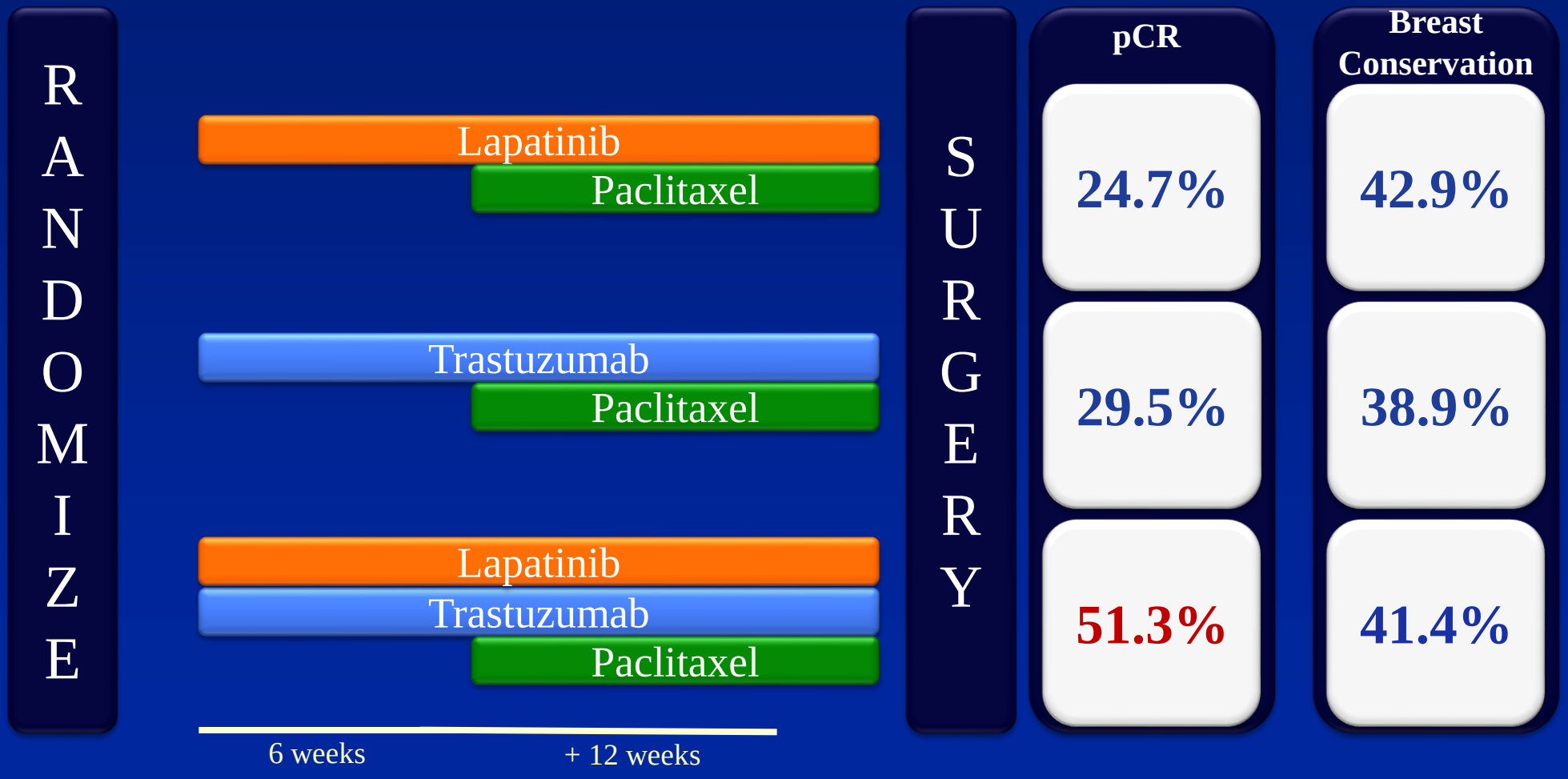
The 3 Most Important Aims in the Treatment of Early Breast Cancer

Improve Outcome

Reduce Morbidity

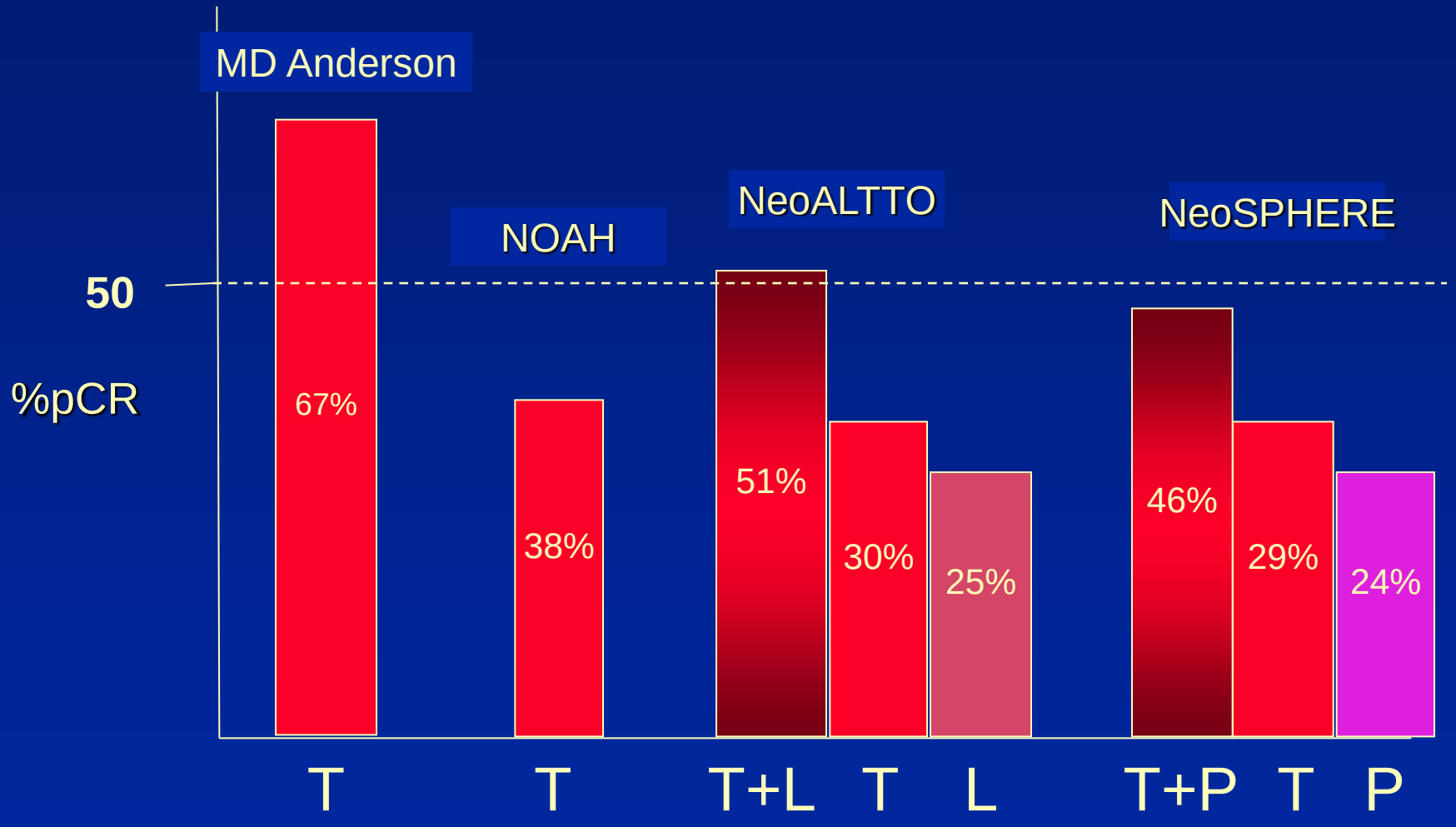
Keep costs down

The discrepancy between high pCR rate and low breast conserving surgery (BCS) following neoadjuvant therapy: analysis from the NeoALTTO trial



Criscitiello et al ESMO 2012; Baselga J et al; Lancet 2012

HER2+ve Breast Cancer: Neoadjuvant anti-HER2 Therapies with CT (pathCR Rates)

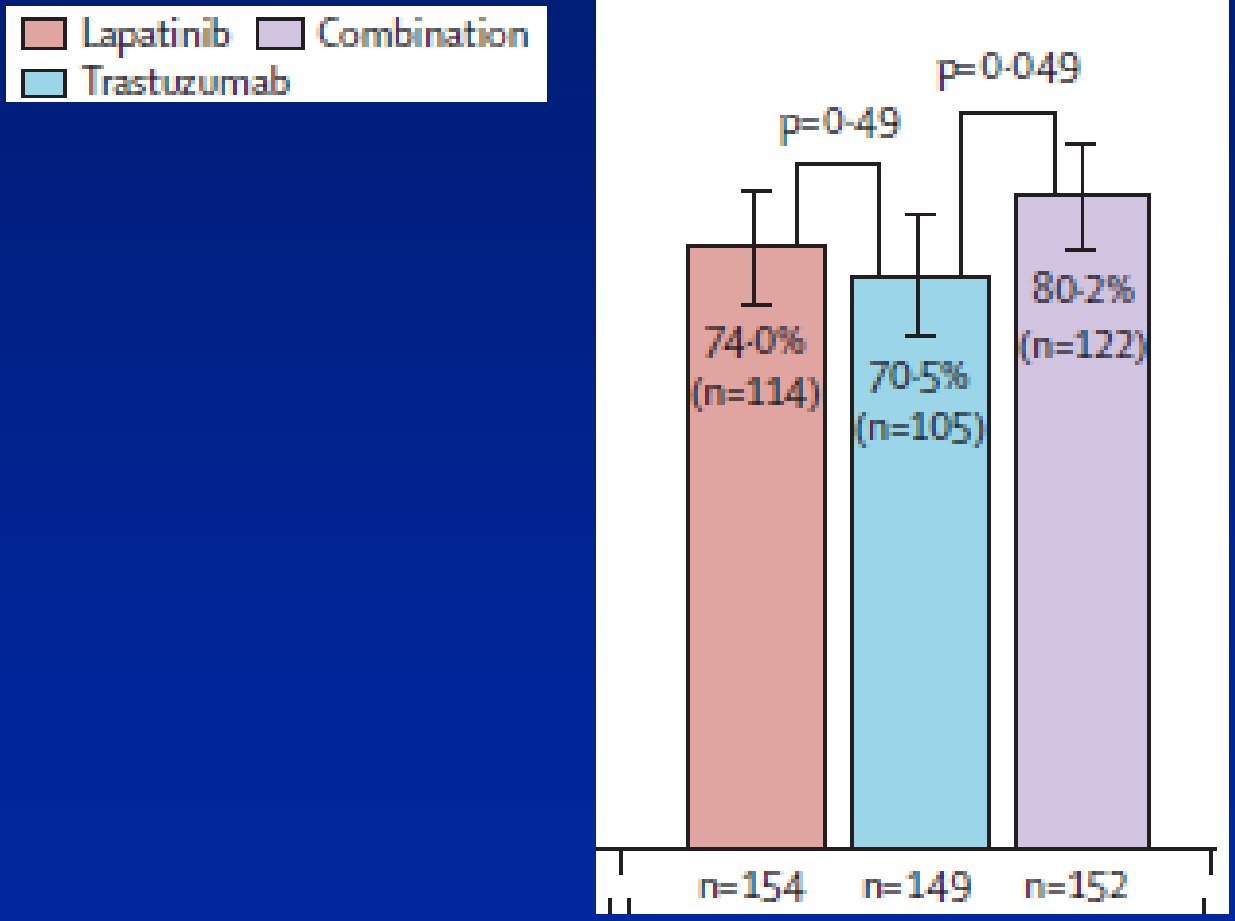


T trastuzumab; L lapatinib; P pertuzumab

The Problem with pCR to Select Choice of Surgery

The surgeon doesn’t know it’s a pCR until after surgery……

Neo-ALTTO Trial
Clinical Response at the time of Surgery



Baselga et al Lancet 2012; 379: 633–40

Factors Influencing Against Breast Conserving Surgery in neoALTTO

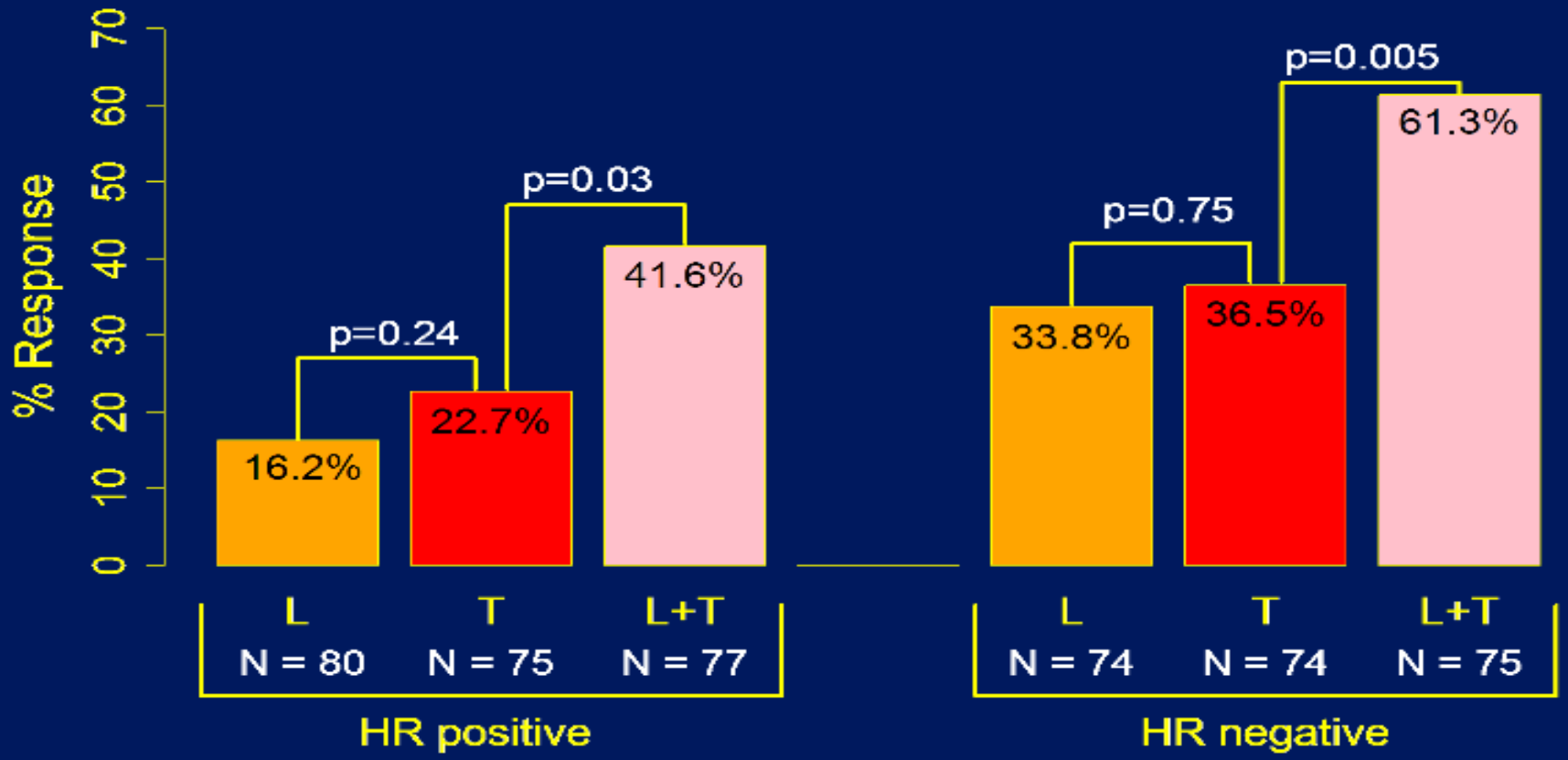
- Surgical plan at diagnosis
- Multicentricity of the tumor
- ER-negative
- Geographic region (less BCS in developing nations)
- Tumor size (less BCS in T3/4)
- Lymph node status (less BCS in clinical N+)
- Invasive lobular

Factors Influencing Against Breast Conserving Surgery in neoALTTO

- Surgical plan at diagnosis
- Multicentricity of the tumor
- **ER-negative**
- Geographic region (less BCS in developing nations)
- Tumor size (less BCS in T3/4)
- Lymph node status (less BCS in clinical N+)
- Invasive lobular

neoALTTO

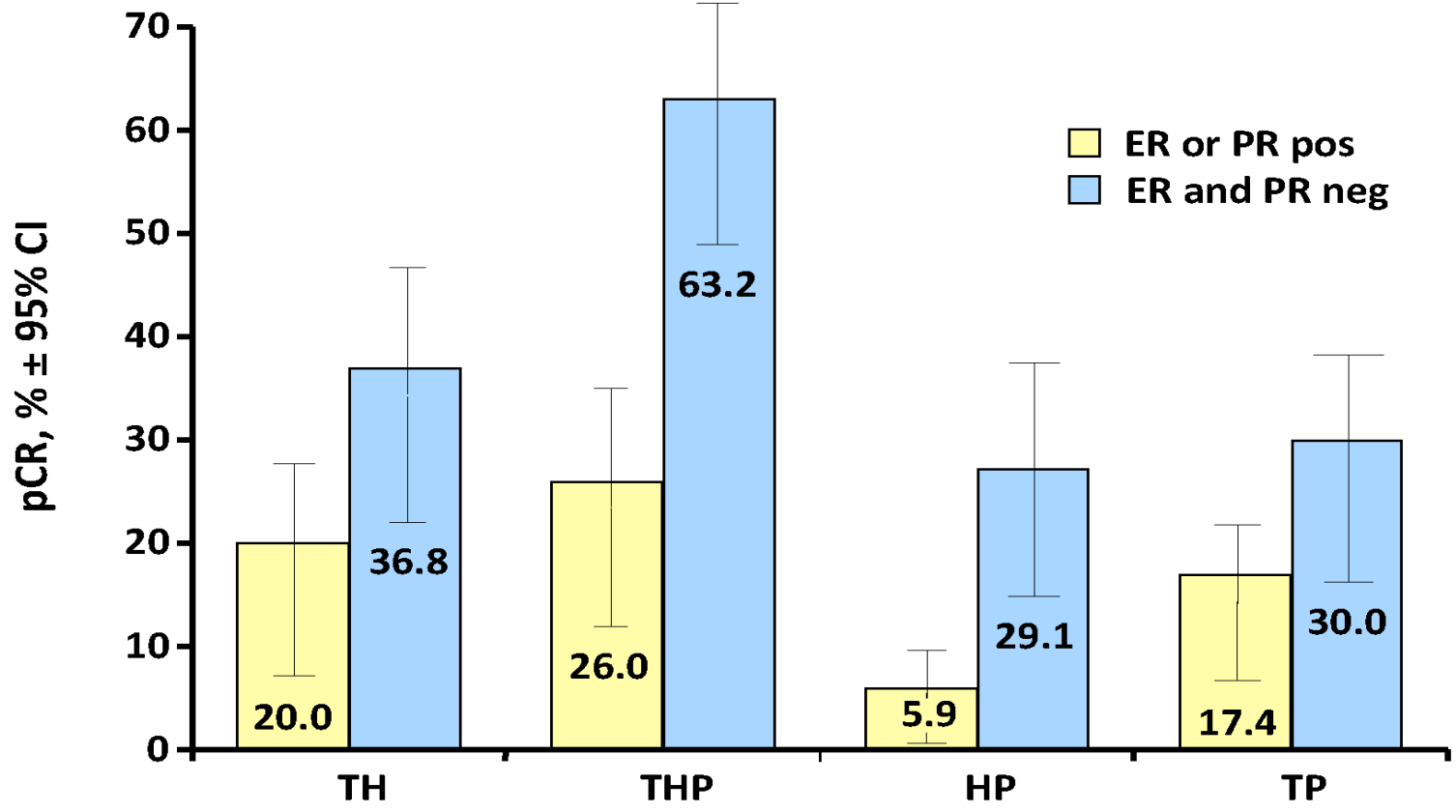
pCR by Hormone Receptor Status



L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response HR: hormone receptors

Baselga et al. SABCS 2011

NeoSphere: pCR and hormone receptors status



H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni et al. SABCS 2011

Neoadjuvant Treatment With Trastuzumab in HER2-Positive Breast Cancer: GeparQuattro Study

- 445pts with operable or locally advanced HER2-positive cancers treated with trastuzumab and chemotherapy.
- pCR rate (no invasive or in situ residual tumors in the breast) 32%,
- Breast conservation rate 63%

Unch et al J Clin Oncol 28 2010

Neoadjuvant Treatment With Trastuzumab in HER2-Positive Breast Cancer: GeparQuattro Study

- Why better?
- Surgeons experienced in, and committed to, the neoadjuvant approach
- But…..

Unch et al J Clin Oncol 28 2010

Neoadjuvant Treatment With Trastuzumab in HER2-Positive Breast Cancer: GeparQuattro Study

- 154 patients had mastectomy
- 21% of these achieved a pCR
- 44% had a maximum tumor diameter of 3 cm at pathologic examination

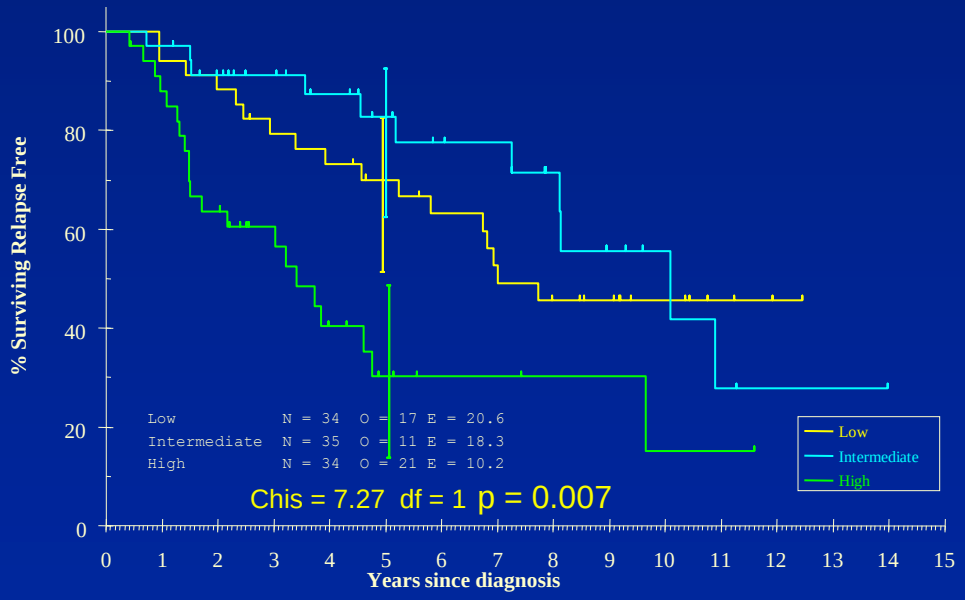
Unch et al J Clin Oncol 28 2010

- But the surgeon doesn’t know it’s a pCR until after surgery…….

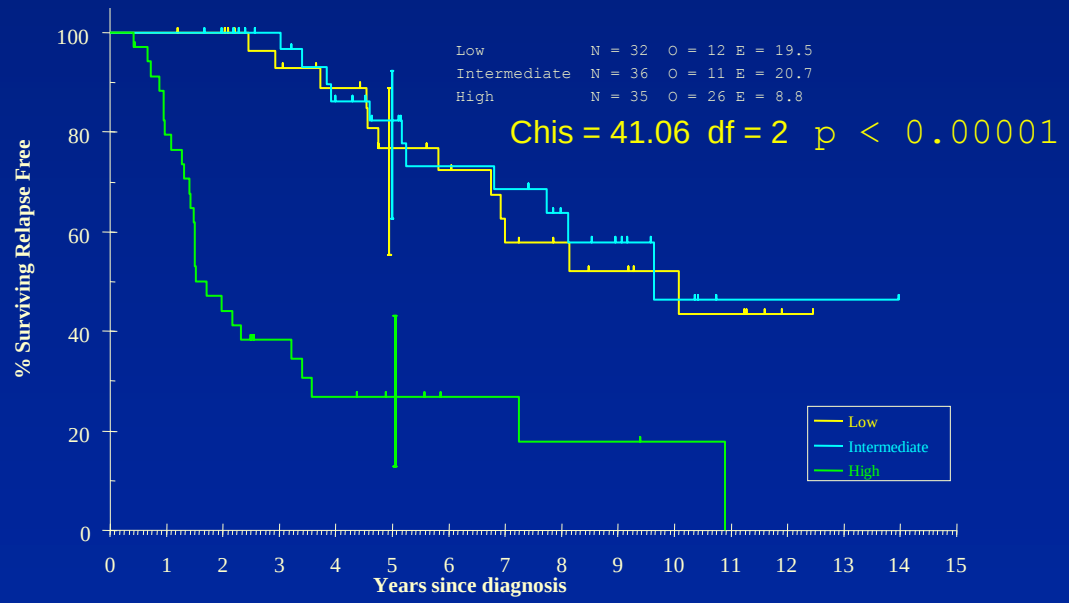
Ki67 Before and After Neoadjuvant Chemotherapy

CT x 6-8 courses

Matched Group: RFS by Ki67 Biopsy Tertile



Matched Group: RFS by Ki67 Excision Tertile

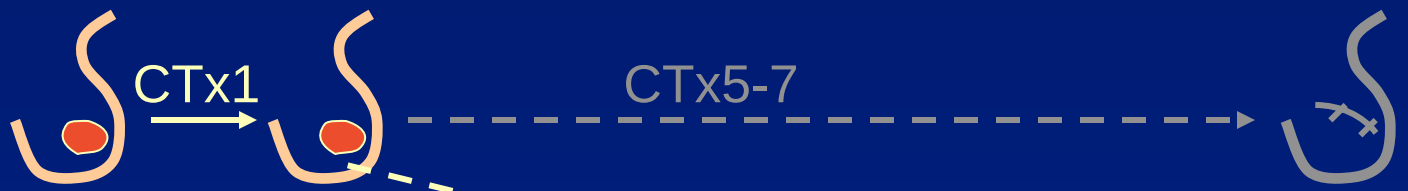


Not significant ← Multivariate → p <0.001*

*the only significant independent predictor

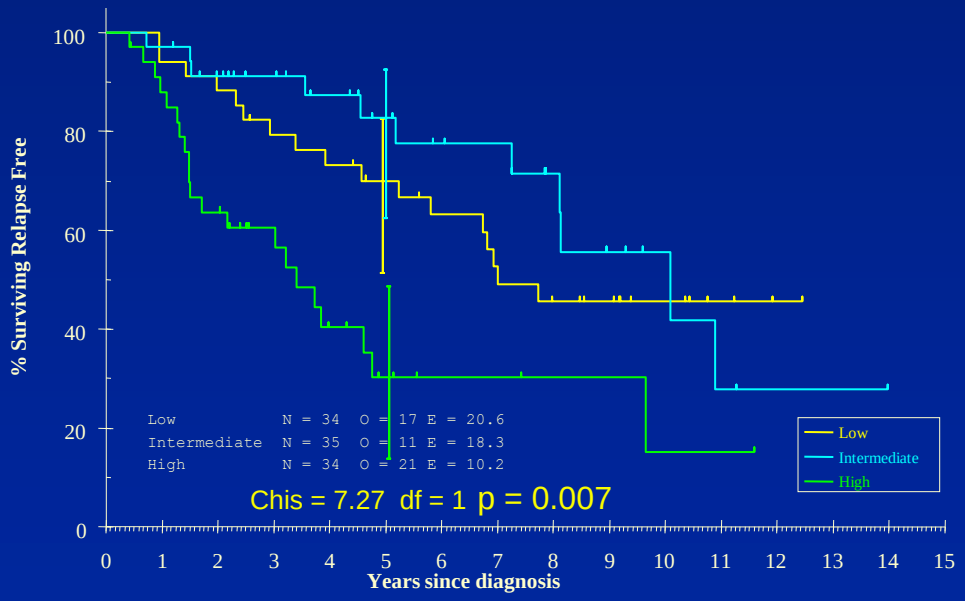
Jones et al Br Ca .Res Treat, 116; 53-68: 2009

Ki67 Before and After Neoadjuvant Chemotherapy

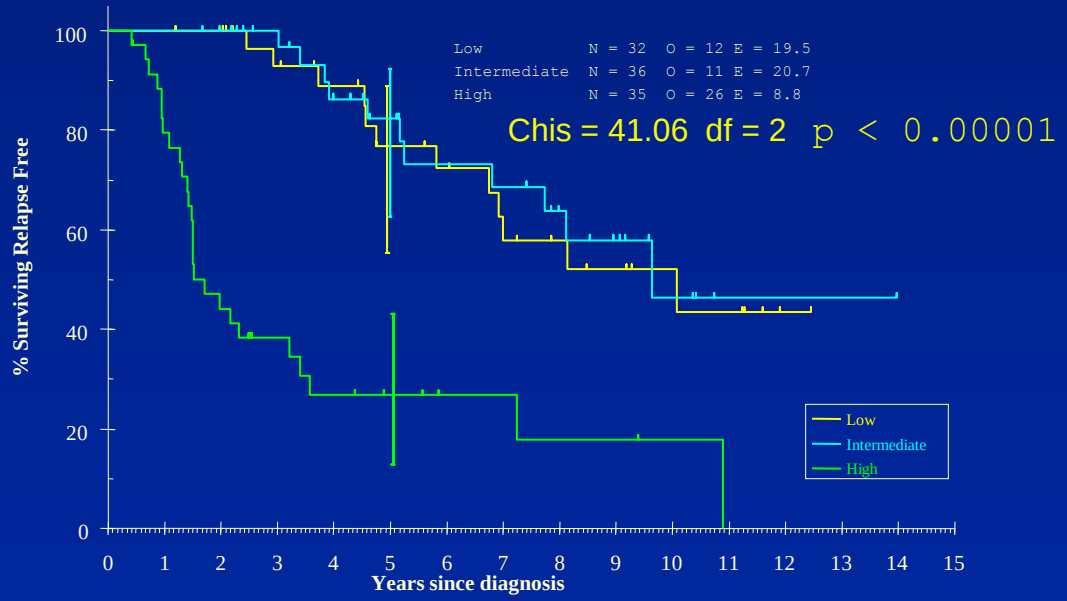


Similar Ki67 changes?

Matched Group: RFS by Ki67 Biopsy Tertile



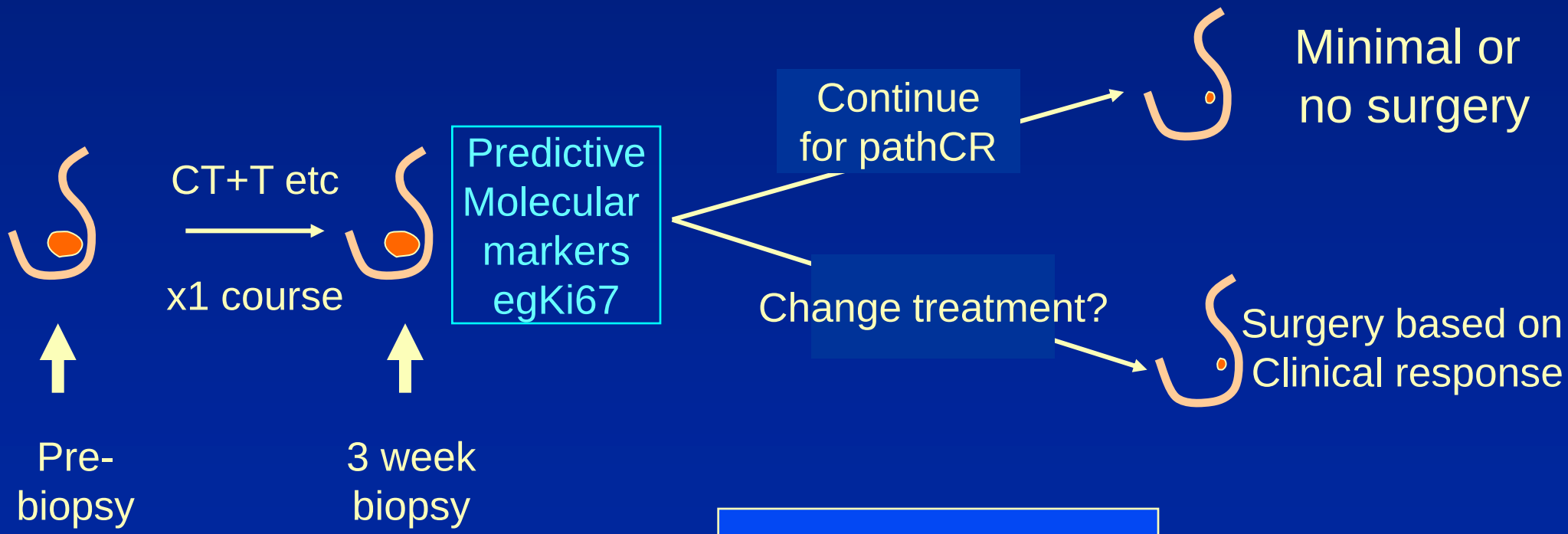
Matched Group: RFS by Ki67 3 week T biopsy tertile



Probably a greater separation since prospective pCRs would be included

HER2+ve Breast Cancer:
A New Neoadjuvant Approach?

Preoperative CT for ALL* appropriate Breast Cancers



*not just large cancers

chemoNEAR

Analysis Between Correlation of Weight Gain at Diagnosis, Weight Gain after Breast Cancer Treatment, and Recurrence in Women with Early Breast Cancer

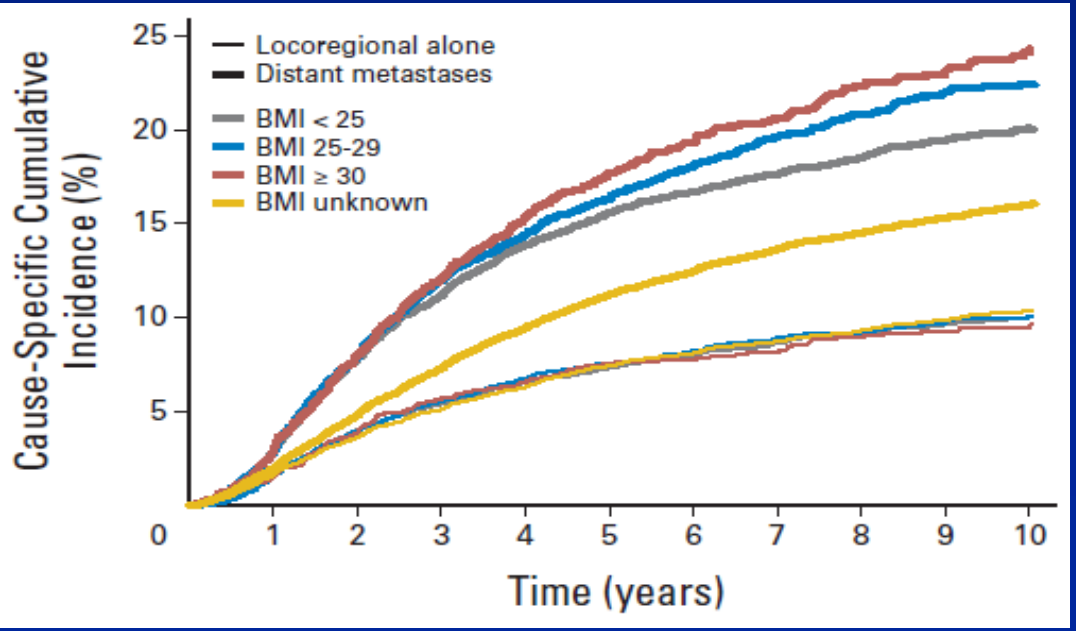
	Body Mass Index						
	At diagnosis			Changes after BC treatment			
	<25 kg/m^2	25-30 kg/m^2	>30 kg/m^2	Loss >1 kg/m^2	Loss <1 kg/m^2	Gain <2 kg/m^2	Gain >2 kg/m^2
No of patients	179	184	157	64	32	185	145
Recurrences	72	73	49	20	15	63	76
p	0.17			0.34		0.0008	

Fedele et al Brindisi, ITALY

Obesity Is an Adverse Prognostic Factor in Early Breast Cancer

Effect of Obesity on Prognosis After Early-Stage Breast Cancer

- 18,967 Danish women with early-stage breast cancer 1977 - 2006
- If BMI 30kg/m2 or more -
- 46% increase in 10yr distant metastases risk
- 38% increase in 30yr breast cancer deaths

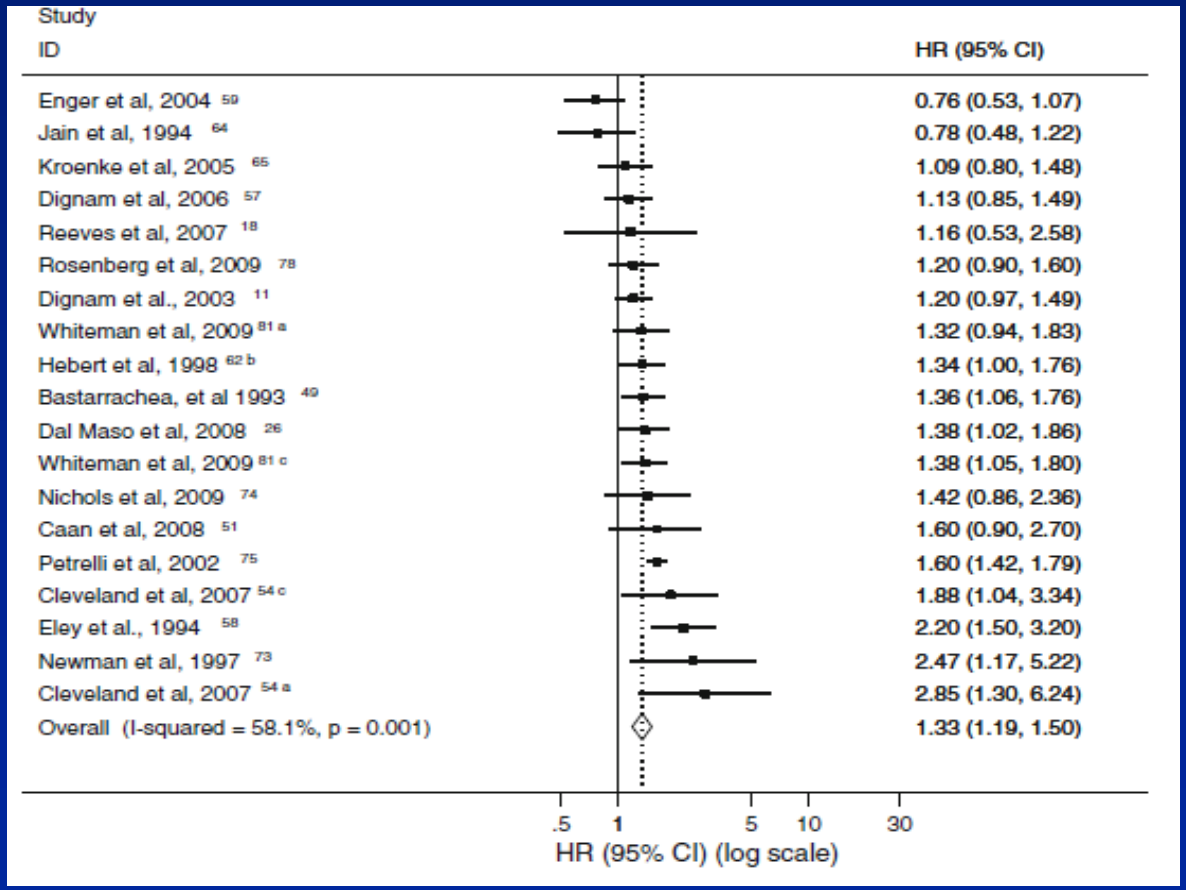


data adjusted for disease characteristics

Ewertz et al J Clin Oncol 29:25-31. 2010

Effect of Obesity on Survival of Women with Breast Cancer: Meta-analysis

- 43 studies 1963-2005
- Prognosis poorer for obesity
- Overall Survival
  HR 1.33 (1.21-1.47)
- BCS* Survival
  HR 1.33 (1.19-1.50)



*Breast cancer specific

Protani et al Breast Cancer Res Treat (2010) 123:627–635

- Does losing weight improve outcome?

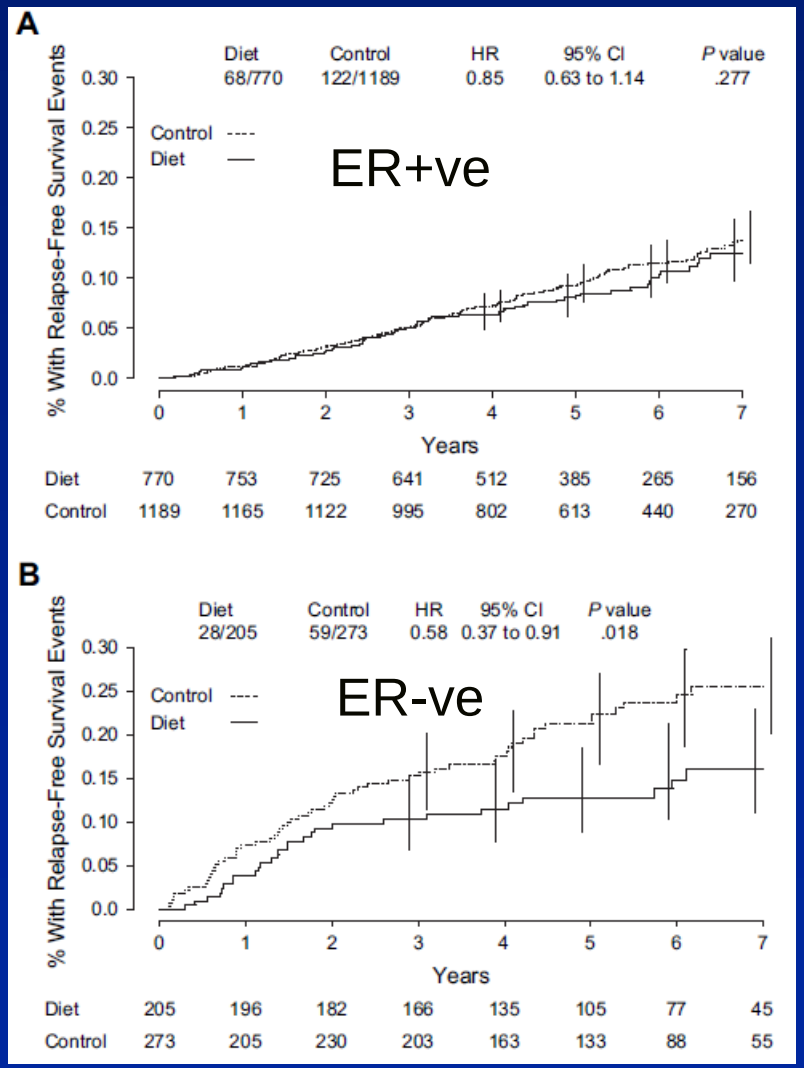
Dietary Fat Reduction and Breast Cancer Outcome: Interim Results From the Women's Intervention Nutrition Study

- Randomized, prospective, multicenter clinical trial 1994 - 2001 in a ratio of 40 : 60
- Dietary intervention (n = 975) v control (n = 1462) groups.
- Interim analysis median followup 60 months
- Dietary fat intake lower in the intervention group (fat grams/day at 12 months, 33.3 v 51.3 (P <.001),
- Significant (P = .005) 6-pound lower mean body weight in the intervention group

Cheblowski et al J Nat.Cancer Inst 2006;98: 1767 – 76

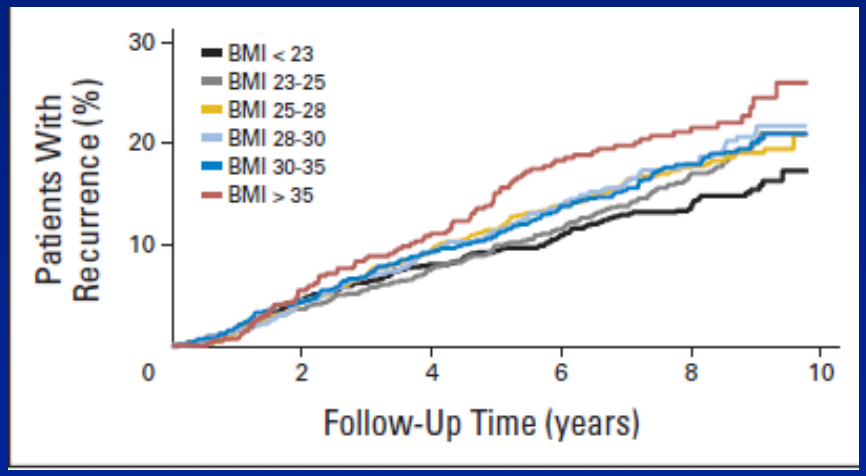
Dietary Fat Reduction and Breast Cancer Outcome: Interim Results From the Women's Intervention Nutrition Study

- 9.8% relapse events* in the dietary group v 12.4% controls.
- HR 0.76 (95% CI = 0.60 to 0.98)
- *P* = .077 for stratified log rank
  P = .034 for adjusted Cox model



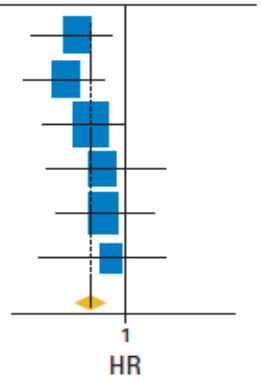
*local, regional, distant, or ipsilateral breast cancer recurrence or new contralateral breast cancer

Body Mass Index and Recurrences after Tamoxifen and Anastrozole: Exploratory Analysis From ATAC



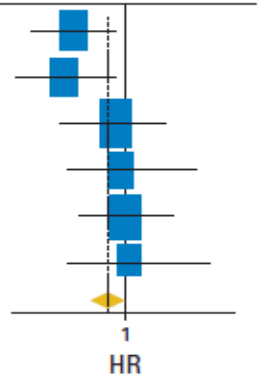
A **All Recurrences**

BMI	Anastrozole No.	Anastrozole %	Tamoxifen No.	Tamoxifen %	HR*	95% CI
< 23	55	11.3	79	16.5	0.64	0.45 to 0.91
23-25	56	13.2	81	20.9	0.58	0.41 to 0.82
25-28	90	15.2	114	19.7	0.76	0.57 to 1.00
28-30	54	16.6	63	19.8	0.83	0.57 to 1.20
30-35	72	16.3	92	19.2	0.84	0.61 to 1.14
> 35	39	19.7	50	21.8	0.76	0.49 to 1.16
All	366	14.8	479	19.4	0.73	0.63 to 0.83



B **Distant Recurrences**

BMI	Anastrozole No.	Anastrozole %	Tamoxifen No.	Tamoxifen %	HR*	95% CI
< 23	38	7.8	59	12.3	0.59	0.39 to 0.89
23-25	38	9.0	59	15.3	0.55	0.36 to 0.83
25-28	71	12.0	71	13.5	0.86	0.62 to 1.19
28-30	42	12.9	44	13.8	0.93	0.61 to 1.42
30-35	63	14.2	70	14.6	0.96	0.68 to 1.36
> 35	35	17.7	35	15.3	0.97	0.61 to 1.57
All	287	11.6	345	14.0	0.79	0.68 to 0.92



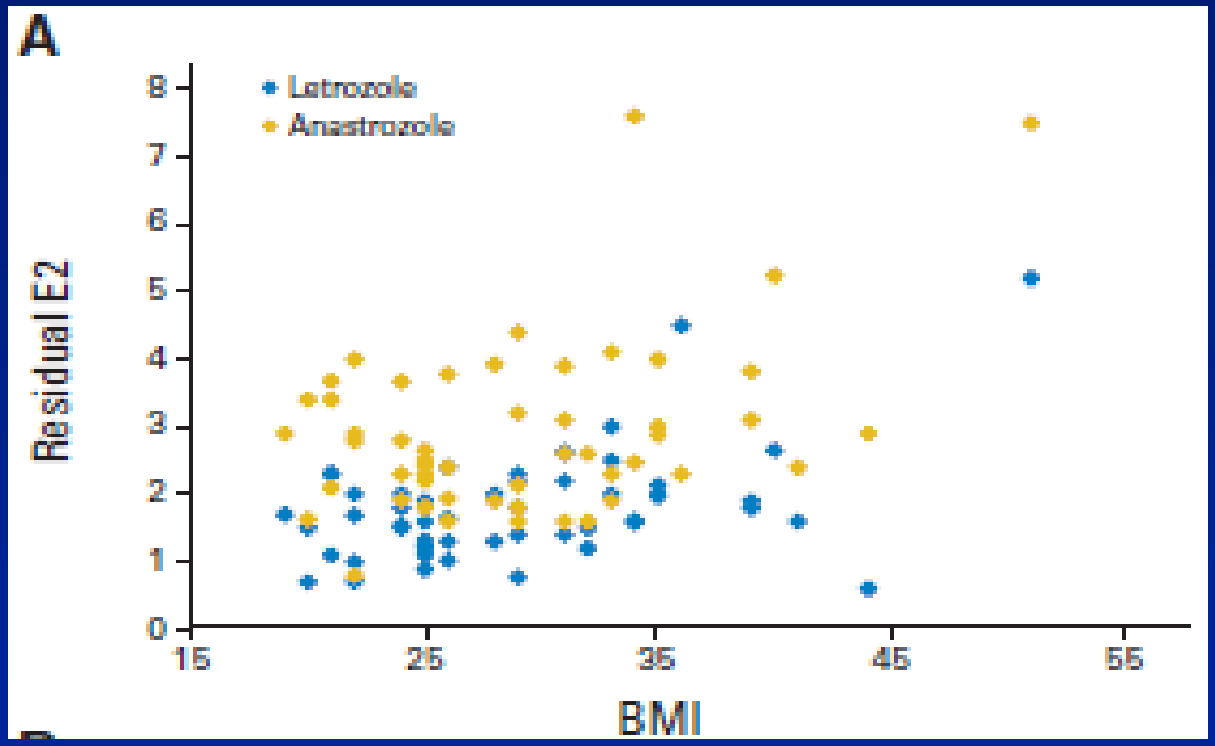
Sestak et al J Clin Oncol 28:3411. 2010

Suppression of Plasma Estrogen Levels by Letrozole and Anastrozole Is Related to Body Mass Index in Patients With Breast Cancer

- 44 postmenopausal patients on anastrozole for 3 months then letrozole for 3 months or vice versa
- Baseline E2 and ES were nearly x3 higher in women with BMIs >35 kg/m2 compared with BMIs <25 kg/m2.
- Letrozole reduced the estradiol levels by an additional 43% and estrone sulfate levels by an additional 58% compared with anastrozole.
- The relative levels of residual estradiol on anastrozole were consistently higher than on letrozole across the entire range of BMIs

Folkherd et al J Clin Oncol 30:2977-2980. © 2012

Suppression of Plasma Estrogen Levels by Letrozole and Anastrozole Related to BMI in Patients With Breast Cancer



On-treatment values (pmol/L) of plasma estradiol after 3 months of treatment with anastrozole or letrozole according to body mass index (BMI).

Folkherd et al J Clin Oncol 30:2977-2980. © 2012

Conclusions

- Reducing Morbidity

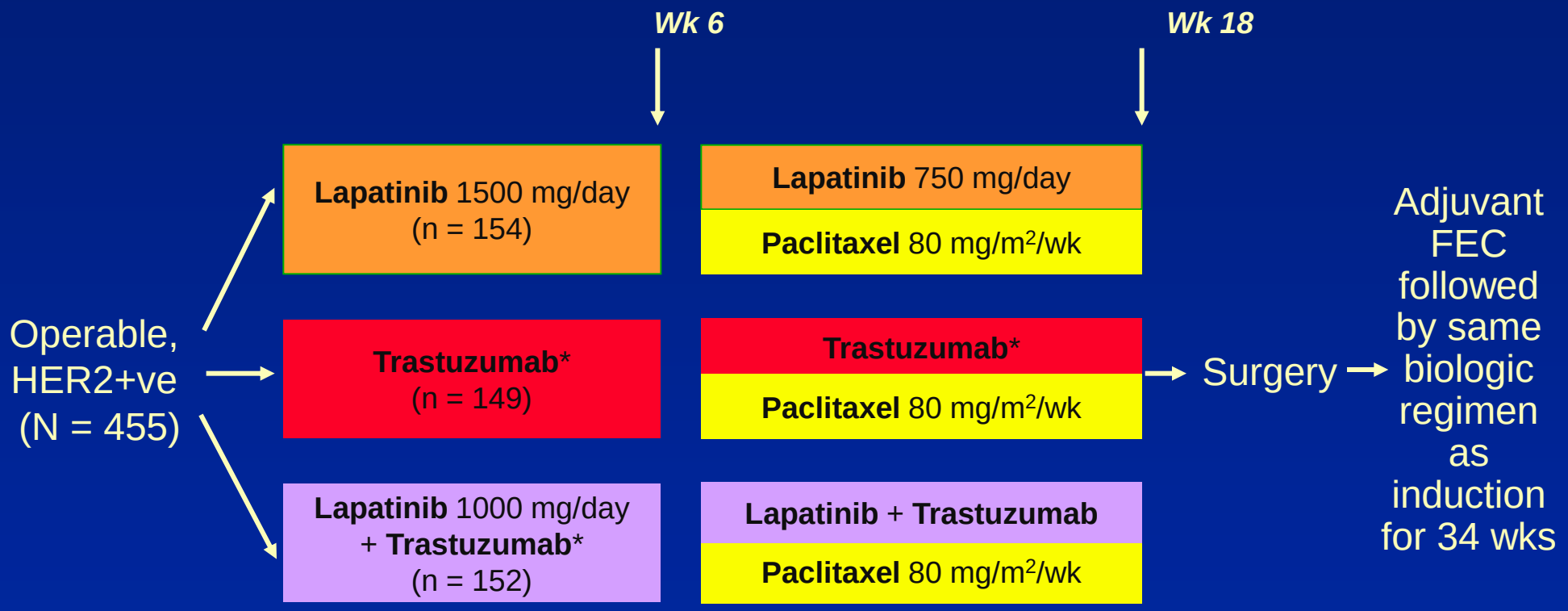
  -We must train our surgeons that most patients with HER2+ve breast cancer do not need mastectomy after neoadjuvant anti- HER2 therapy with CT

  -We need to explore short term changes in molecular markers to predict who really needs mastectomy

- Improving Outcome at Reduced Cost

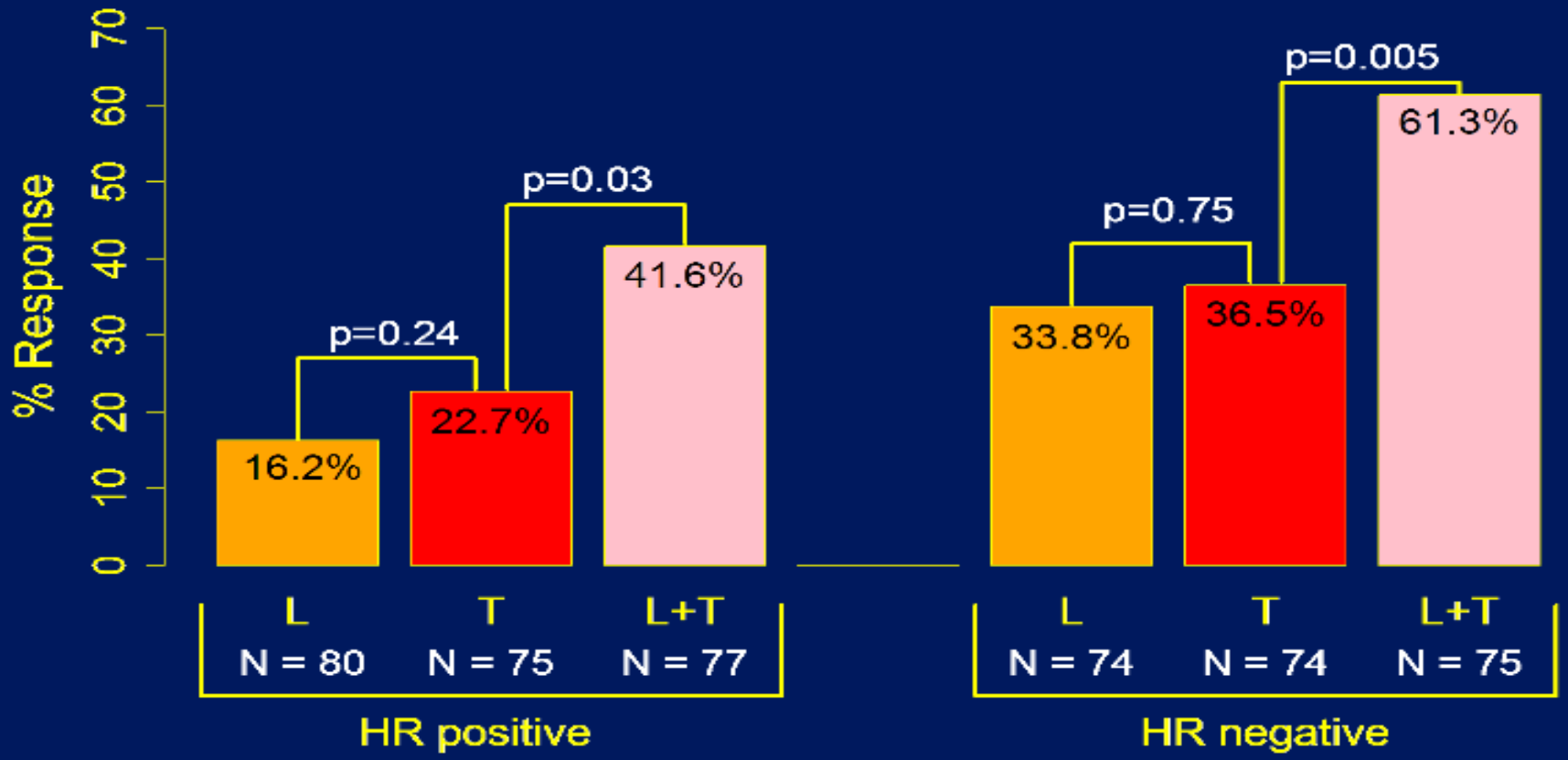
  -We must emphasise strongly to our patients that not gaining/ losing weight after treatment is an important (and very resource efficient) way to reduce the risk of recurrence, in addition to adjuvant therapy

NeoALLTO: Neoadjuvant Lapatinib, Trastuzumab, or Combination With Paclitaxel in HER2+ EBC



Baselga J, et al. SABCS 2010. Abstract S3-3.

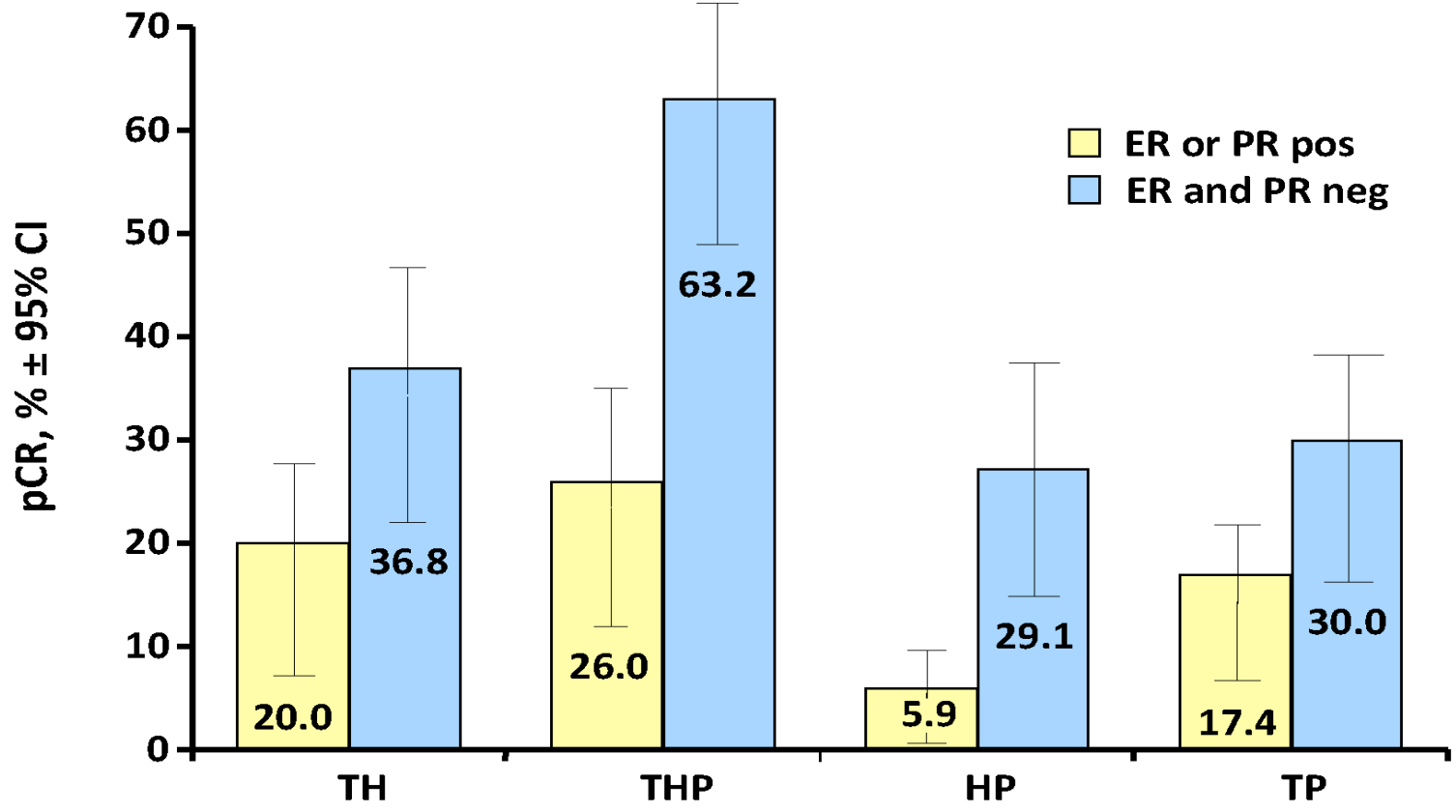
pCR by Hormone Receptor Status



L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response HR: hormone receptors

Baselga et al. SABCS 2011

NeoSphere: pCR and hormone receptors status



H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni et al. SABCS 2011

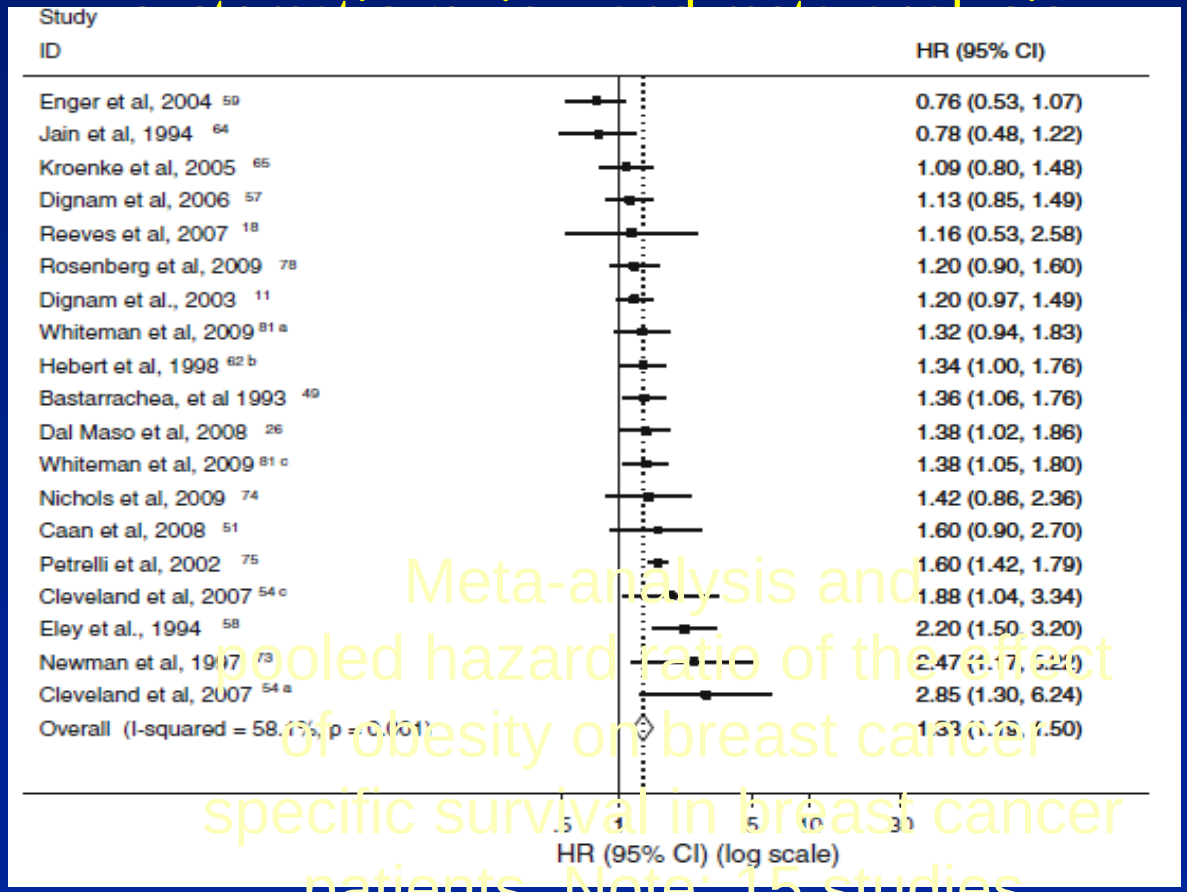
- But the surgeon doesn’t know it’s a pCR until after surgery…….

Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis

- Abstract Obesity is a risk factor for the development of
- new cases of breast cancer and also affects survival in
- women who have already been diagnosed with breast cancer.
- Early studies of obesity and breast cancer survival have
- been summarised in two meta-analyses, but the latest of
- these only included studies that recruited women diagnosed
- as recently as 1991. The primary aim of this study was to
- conduct a meta-analysis that included the more recent
- studies. A systematic search of MEDLINE, EMBASE and
- CINAHL was conducted to identify original data evaluating
- the effects of obesity on survival in newly diagnosed breast
- cancer patients. Adjusted hazard ratios (HR) from individual
- studies were pooled using a random effects model. A series
- of pre-specified sensitivity analyses were conducted on
- factors such as overall versus breast cancer survival and
- treatment versus observational cohort. The meta-analysis
- included 43 studies that enrolled women diagnosed with
- breast cancer between 1963 and 2005. Sample size ranged
- from 100 to 424168 (median 1192). The meta-anal
- showed poorer survival among obese compared with nonobese

Protani et al Breast Cancer Res Treat (2010) 123:627–635

Effect of obesity on survival of women with breast cancer:

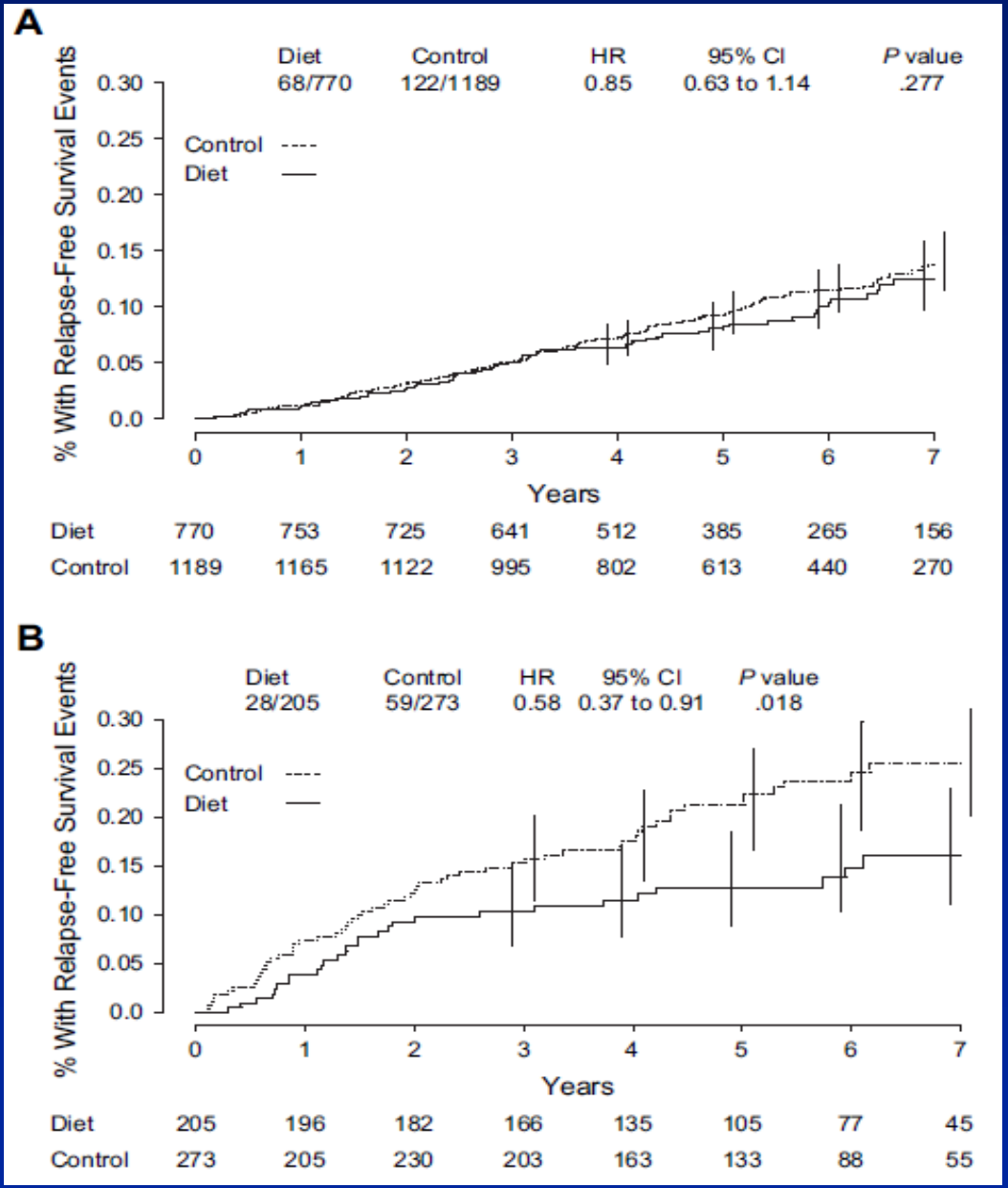


Meta-analysis and pooled hazard ratio of the effect of obesity on breast cancer specific survival in breast cancer patients. Note: 15 studies provided 16 estimates. a Premenopausal women only, b study reported HR per one

Dietary Fat Reduction and Breast Cancer Outcome: Interim Effi cacy Results From the Women's Intervention Nutrition Study

- **randomized, prospective, multicenter clinical trial to test**
- **the effect of a dietary intervention designed to reduce fat**
- **intake in women with resected, early-stage breast cancer**
- **2437 women were randomly assigned between**
- **February 1994 and January 2001 in a ratio of 40 : 60 to**
- **dietary intervention (n = 975) or control (n = 1462) groups.**
- **An interim analysis was performed after a median followup**
- **of 60 months when funding for the intervention ceased.**
- **Mean differences between dietary intervention and control**
- **groups in nutrient intakes and anthropometric variables**
- **were compared with *t* tests. Relapse-free survival was examined**
- **using Kaplan – Meier analysis, stratifi ed log-rank tests,**
- **and Cox proportional hazards models. Statistical tests were**
- **two-sided.**

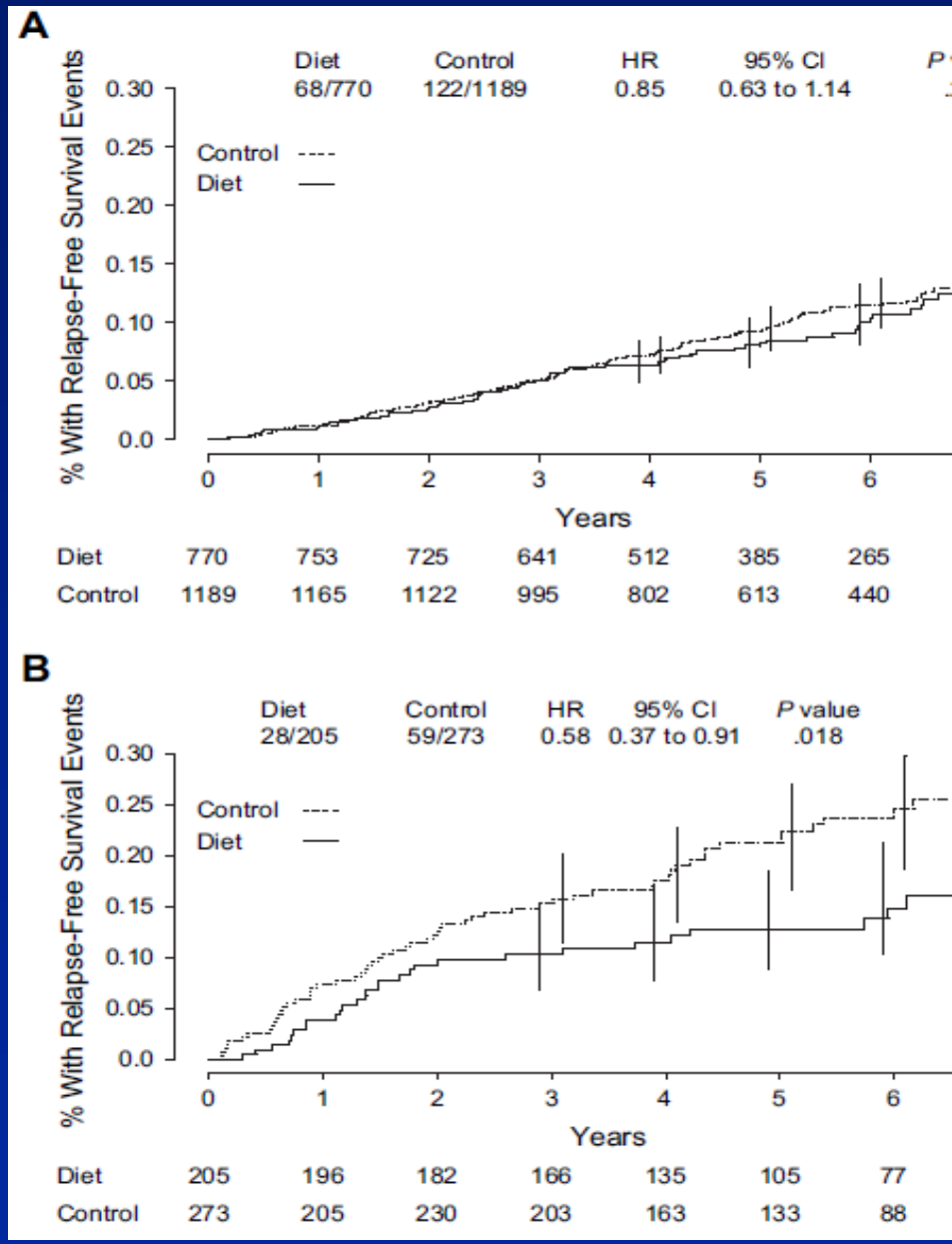
Cheblowski et al J Natl Cancer Inst 2006;98: 1767 – 76



Results: **Dietary fat intake was lower in the inter than in the control group (fat grams/day at months, 33.3 [95% confi dence interval {CI} = 32.2 versus 51.3 [95% CI = 50.0 to 52.7], respectively; corresponding to a statistically signifi cant (*P* = 6-pound lower mean body weight in the interventi A total of 277 relapse events (local, regional, distant, breast cancer recurrence or new contralateral cancer) have been reported in 96 of 975 (9.8%) w the dietary group and 181 of 1462 (12.4%) wome control group. The hazard ratio of relapse event intervention group compared with the control gr 0.76 (95% CI = 0.60 to 0.98, *P* = .077 for stratifi ed and *P* = .034 for adjusted Cox model analysis). Ex analyses suggested a differential effect of the dietary based on hormonal receptor status.**

Results:.

277 relapse events (local, regional, distant, or ipsilateral
ast cancer recurrence or new contralateral breast
er) have been reported in 96 of 975 (9.8%) women in
ietary group and 181 of 1462 (12.4%) women in the
rol group. The hazard ratio of relapse events in the
vention group compared with the control group was
95% CI = 0.60 to 0.98, *P* = .077 for stratifi ed log rank
= .034 for adjusted Cox model analysis). Exploratory
suggested a differential effect of the dietary intervention
based on hormonal receptor status.



Plan

- Obesity linked to BC risk in post men but not premen KPritchard's editorial for discussion
- Obesity linked to poor outcome- ATAC etc Good review start of BIG 1-98 paper
- Relative role of AIs
- This paper shows that simply not gaining wt may help
- Check Tony Howell's data and Slebowski's

- Intro to both papers –simple ways to improve outcome / minimise morbidity in bc without lots of expense

Effect of Obesity on Prognosis After Early-Stage Breast Cancer

body mass index (BMI) at diagnosis available for 18,967 (35%) of 53,816 women treated for early-stage breast cancer in Denmark 1977 - 2006

follow-up for first events up to 10 years and for death up to 30 years

Results

Adjusted risk of distant metastases after 10 years was significantly increased by 46%, and the risk of breast cancer deaths after 30 years was significantly increased by 38% for patients with a BMI of 30 kg/m2 or more.

BMI had no influence on the risk of locoregional recurrences.

Chemotherapy and endocrine therapy seemed to be less effective after 10 or more years for patients with BMIs greater than 30 kg/m2.

Conclusion

Obesity is an independent prognostic factor for developing distant metastases and for death as a result of breast cancer; the effects of adjuvant therapy seem to be lost more rapidly in patients with breast cancer and obesity.

Ewertz et al J Clin Oncol 29:25-31. 2010

Effect of Obesity on Prognosis After Early-Stage Breast Cancer

- **Patients and Methods**
- BMI at diagnosis was available for 18,967 women with early-stage breast cancer in Denmark between 1977 and 2006 with complete
- 10 years FU first events 30yr FU deaths
- When data were adjusted for disease characteristics, the risk of developing distant metastases after 10 years was significantly increased by 46%, and the risk of dying as a result of breast cancer after 30 years was significantly
- increased by 38% for patients with a BMI of 30 kg/m2 or more.

- BMI had no influence on the risk
- of locoregional recurrences. Both chemotherapy and endocrine therapy seemed to be less
- effective after 10 or more years for patients with BMIs greater than 30 kg/m2.
- **Conclusion**
- Obesity is an independent prognostic factor for developing distant metastases and for death as a
- result of breast cancer; the effects of adjuvant therapy seem to be lost more rapidly in patients
- with breast cancer and obesity.

Ewertz et al J Clin Oncol 29:25-31. 2010

Effect of Obesity on Prognosis After Early-Stage Breast Cancer

- **Purpose**
- This study was performed to characterize the impact of obesity on the risk of breast cancer
- recurrence and death as a result of breast cancer or other causes in relation to adjuvant treatment.
- **Patients and Methods**
- Information on body mass index (BMI) at diagnosis was available for 18,967 (35%) of 53,816
- women treated for early-stage breast cancer in Denmark between 1977 and 2006 with complete
- follow-up for first events (locoregional recurrences and distant metastases) up to 10 years and for
- death up to 30 years. Information was available on prognostic factors and adjuvant treatment for
- all patients. Univariate analyses were used to compare the associations of known prognostic
- factors and risks of recurrence or death according to BMI categories. Cox proportional hazards
- regression models were used to assess the influence of BMI after adjusting for other factors.
- **Results**
- Patients with a BMI of 30 kg/m2 or more were older and had more advanced disease at diagnosis
- compared with patients with a BMI below 25 kg/m2 (*P* .001). When data were adjusted for
- disease characteristics, the risk of developing distant metastases after 10 years was significantly
- increased by 46%, and the risk of dying as a result of breast cancer after 30 years was significantly
- increased by 38% for patients with a BMI of 30 kg/m2 or more. BMI had no influence on the risk
- of locoregional recurrences. Both chemotherapy and endocrine therapy seemed to be less
- effective after 10 or more years for patients with BMIs greater than 30 kg/m2.
- **Conclusion**
- Obesity is an independent prognostic factor for developing distant metastases and for death as a
- result of breast cancer; the effects of adjuvant therapy seem to be lost more rapidly in patients
- with breast cancer and obesity.

Ewertz et al J Clin Oncol 29:25-31. 2010

Suppression of Plasma Estrogen Levels by Letrozole and Anastrozole Is Related to Body Mass Index in Patients With Breast Cancer

- 44 postmenopausal patients on anastrozole for 3 months
- then letrozole (2.5 mg per day) for 3 months or vice versa
- **Results**
- Baseline values of estradiol and estrone sulfate were significantly correlated with BMI (*r* 0.57;
- *P* .001, and *r* 0.38; *P* .006, respectively). Levels of estrogen in patients receiving treatment
- were greater at higher levels of BMI with both AIs, but although this was significant with letrozole
- (*r* 0.35; *P* .013, and *r* 0.30; *P* .035 for estradiol and estrone sulfate, respectively), it was
- not with anastrozole. Suppression of both estrogen types was greater with letrozole across the full
- range of BMIs in this study.
- **Conclusion**
- The suppressed levels of plasma estradiol and estrone sulfate in postmenopausal women with
- early ER-positive breast cancer treated with the AIs anastrozole and letrozole are related to BMI.

Folkherd et al J Clin Oncol 30:2977-2980.

Suppression of Plasma Estrogen Levels by Letrozole and Anastrozole Is Related to Body Mass Index in Patients With Breast Cancer

- **Purpose**
- To investigate whether suppression of plasma estradiol and estrone sulfate levels by the aromatase inhibitors (AIs) anastrozole and letrozole is related to body mass index (BMI) in postmenopausal women with early estrogen receptor (ER) –positive breast cancer. Recent studies have reported that the AI anastrozole has lower effectiveness than tamoxifen in women with high BMI. This effect with high BMI might hypothetically be a result of reduced inhibition of aromatase and suppression of plasma estrogen levels and might be overcome by the use of an increased dose of anastrozole or, alternatively, the use of a more potent AI such as letrozole.
- **Patients and Methods**
- Plasma estradiol and estrone sulfate levels from a highly sensitive radioimmunoassay were available for 44 postmenopausal patients who received anastrozole (1 mg per day) for 3 months followed by letrozole (2.5 mg per day) for 3 months or the opposite sequence. Correlations between the estrogen suppression by each AI and BMI were assessed.
- **Results**
- Baseline values of estradiol and estrone sulfate were significantly correlated with BMI (r 0.57; P .001, and r 0.38; P .006, respectively). Levels of estrogen in patients receiving treatment were greater at higher levels of BMI with both AIs, but although this was significant with letrozole (r 0.35; P .013, and r 0.30; P .035 for estradiol and estrone sulfate, respectively), it was not with anastrozole. Suppression of both estrogen types was greater with letrozole across the full range of BMIs in this study.
- **Conclusion**
- The suppressed levels of plasma estradiol and estrone sulfate in postmenopausal women with early ER-positive breast cancer treated with the AIs anastrozole and letrozole are related to BMI.

Folkherd et al J Clin Oncol 30:2977-2980.

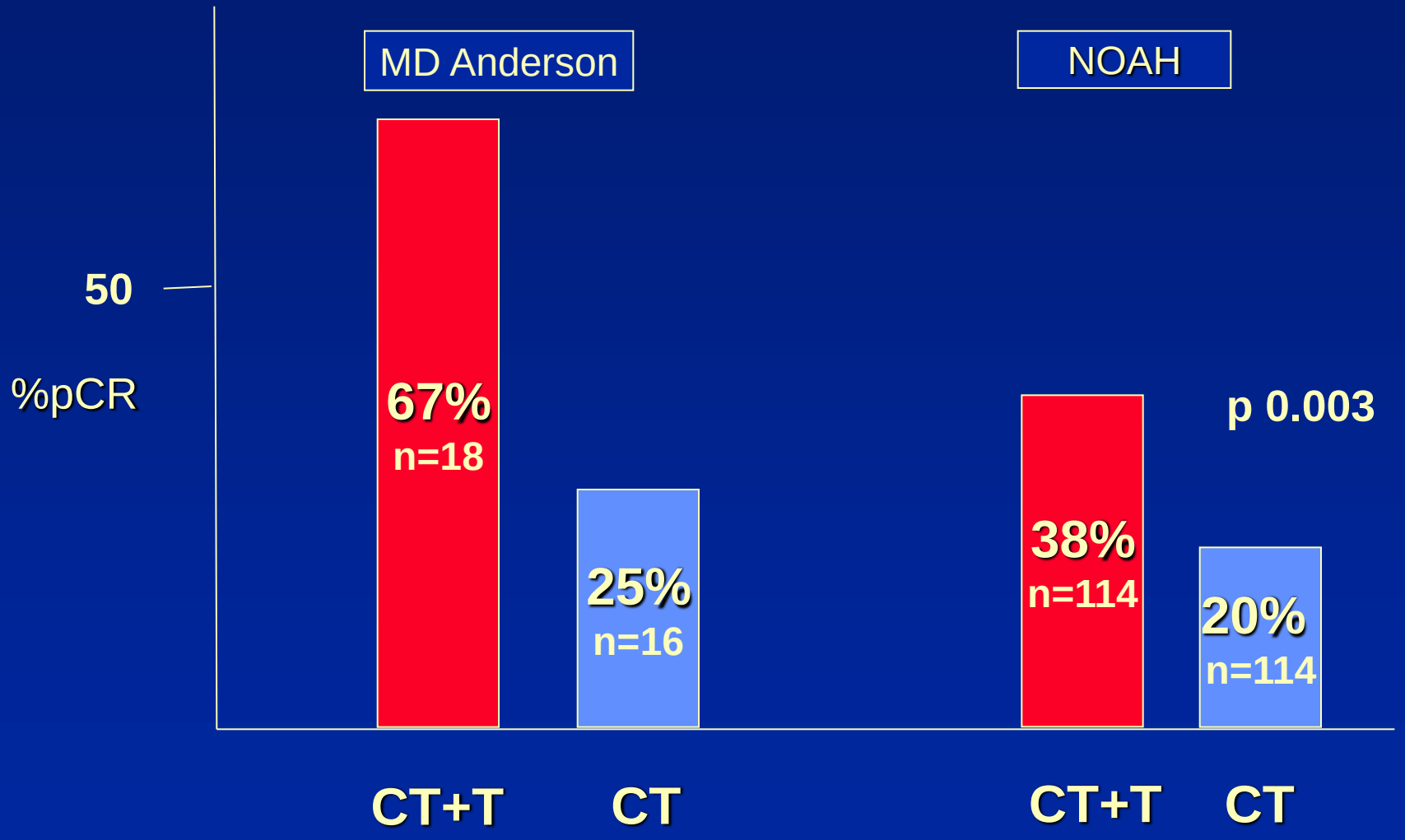
The discrepancy between high pathological complete response (pCR) rate and low breast conserving surgery (BCS) following neoadjuvant therapy: analysis from the NeoALTTO trial (BIG 1-06)

Carmen Criscitiello, Hatem A. Azim Jr., Dominique Agbor-Tarh, Evandro de Azambuja, Martine J. Piccart, José Baselga, Holger Eidtmann, Serena Di Cosimo, Ian Bradbury, Isabel T. Rubio

on behalf of the Neo-ALTTO Study Team

September 30, 2012

HER2+ve Breast Cancer: Neoadjuvant CT ± Trastuzumab (pathCR Rates)



Buzdar A, et al. JCO 200

Gianni et al ASCO 2007

Neoadjuvant Treatment With Trastuzumab in HER2-Positive Breast Cancer: GeparQuattro Study

- 154 patients had mastectomy
- 20% achieved a complete response before surgery
- 21% achieved a pCR
- 44% had a maximum tumor diameter of 3 cm at pathologic examination

Unch et al J Clin Oncol 28 2010

Why Use Neoadjuvant Therapy?

- To prolong survival
- To downstage to avoid mastectomy
- To identify short term molecular markers to predict long term outcome for individual patients

Why Use Neoadjuvant Therapy?

- To prolong survival
- To downstage to avoid mastectomy
- To identify short term molecular markers to predict long term outcome for individual patients