Taking Neoadjuvant Treatment into the Clinic
The Data and the Challenges

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Neoadjuvant Therapy

- Issue of locally advanced breast cancer vs operable breast cancer and appropriateness of neoadjuvant therapy
- Understanding the differential responses to therapy by subtype
- Following the neoadjuvant patient for response
- Local therapy considerations
- Referral patterns, multidisciplinary care

Neoadjuvant (Preoperative) Therapy

Adjuvant

Surgery → Systemic therapy

Neoadjuvant

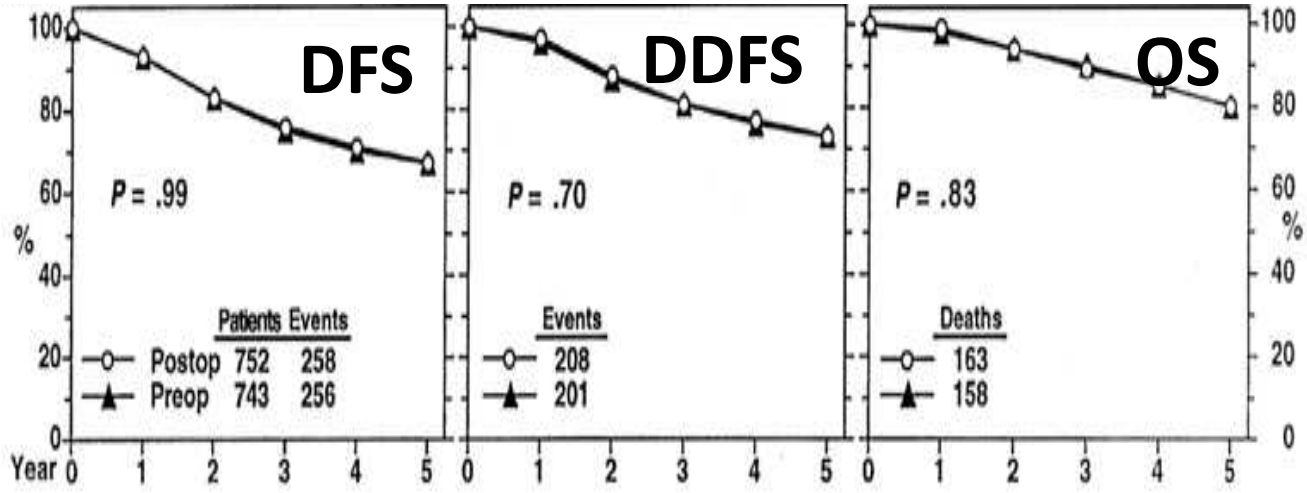
Systemic therapy → Surgery

NSABP B-18: Preop versus postop AC:

N=1450
clinical T1-3, N0-1

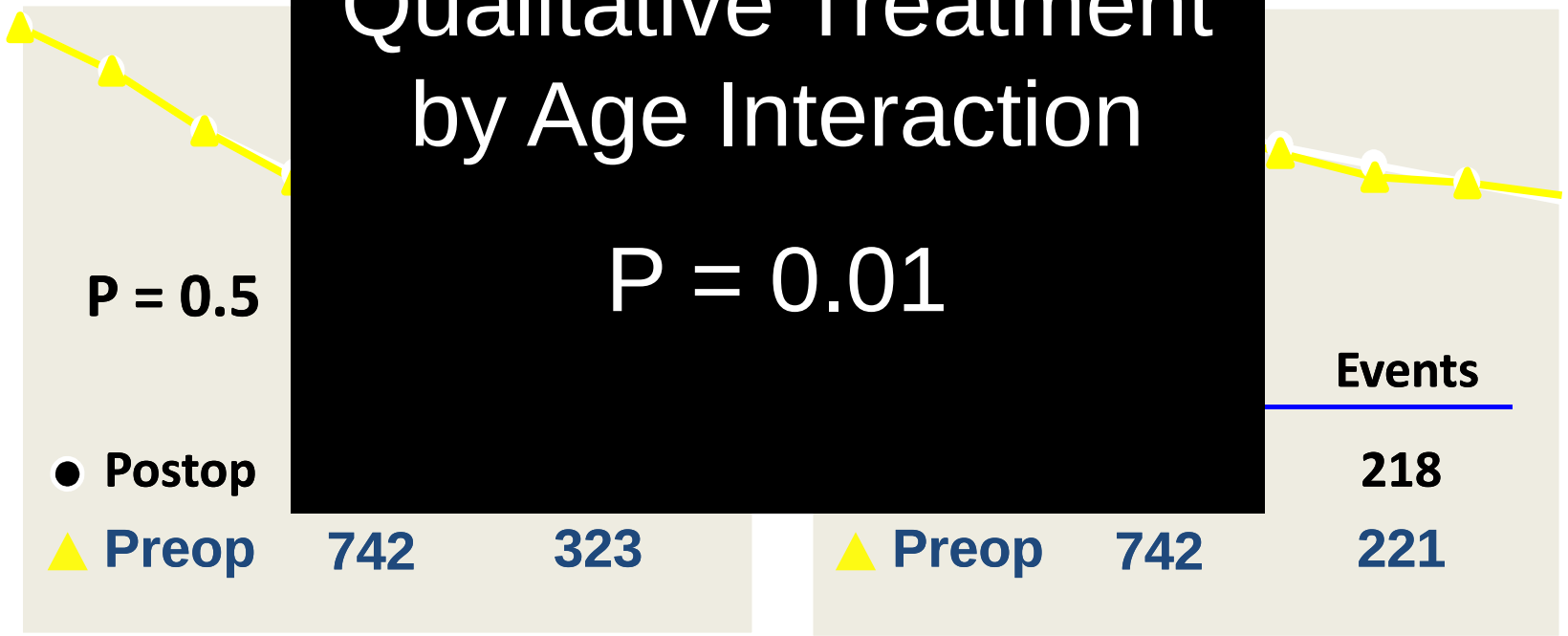
AC → OR

OR → AC



Fisher B et al, JCO 1998

Dis vival



Qualitative Treatment by Age Interaction

P = 0.01

Wolmark N: CDC, 2000

B18 Results

- No significant difference in outcomes gave reassurances that either order was safe
- There was a trend however in younger women for a better outcome with neoadjuvant therapy
- Was young age a surrogate for HER2+ or TNBC in the era prior to understanding subtypes?

Pathologic Response to Chemotherapy by Subtype

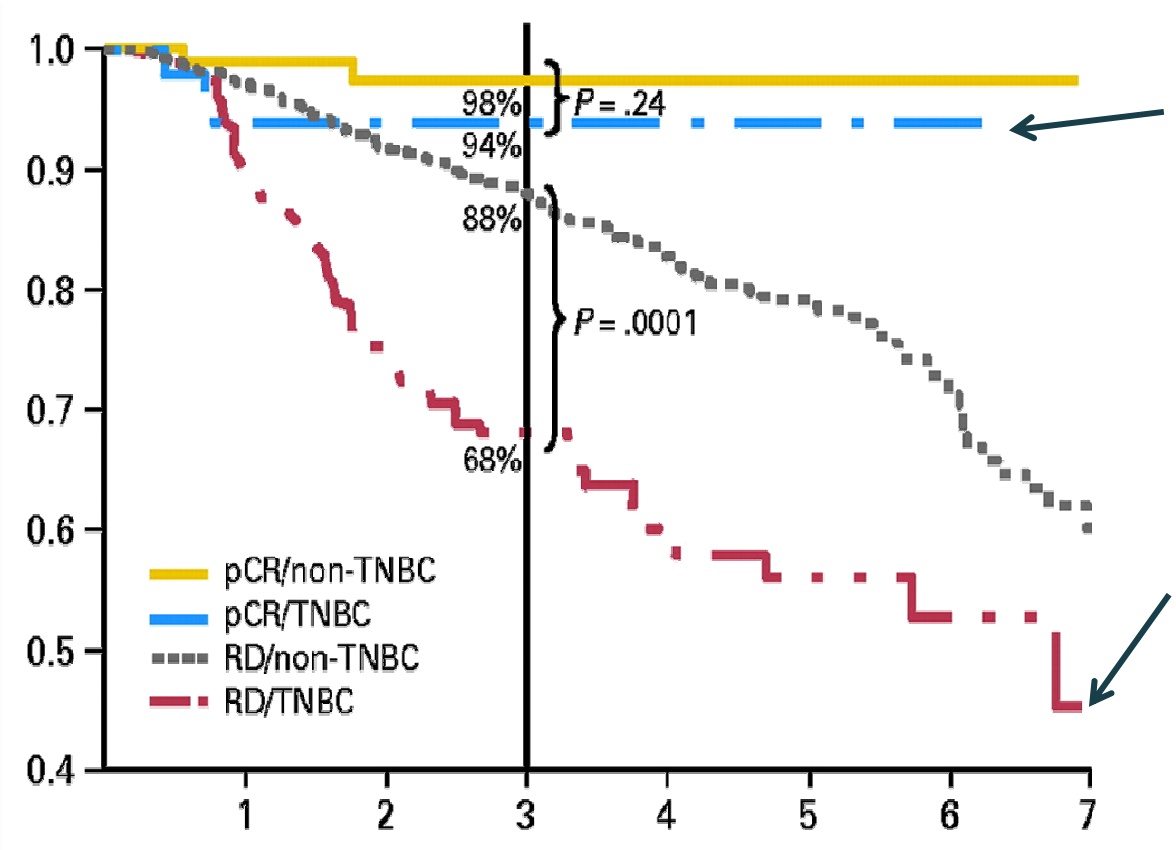
Modified PAM50 subtyping in 360 patients treated with anthracycline/taxane chemotherapy only (no trastuzumab!)

Overall pCR rate = 22%

Classification	Residual disease	Pathologic complete response (pCR)
Basal-like	**47 (58%)**	**34 (42%)**
Claudin-low	**29 (67%)**	**14 (33%)**
HER2-enriched	**31 (63%)**	**18 (37%)**
LumA	**110 (98%)**	**2 (2%)**
LumB	**56 (85%)**	**10 (15%)**
Normal-like	**13 (76%)**	**4 (24%)**

Courtesy C. Perou

Responsiveness to Conventional Chemotherapy



Basal-like / triple negative:

Often responsive

If pCR achieved = good outcome!

Nonresponse = poor outcome

Clinical Impact of Neoadjuvant Therapy

Disease-free and overall survival unrelated to sequence.

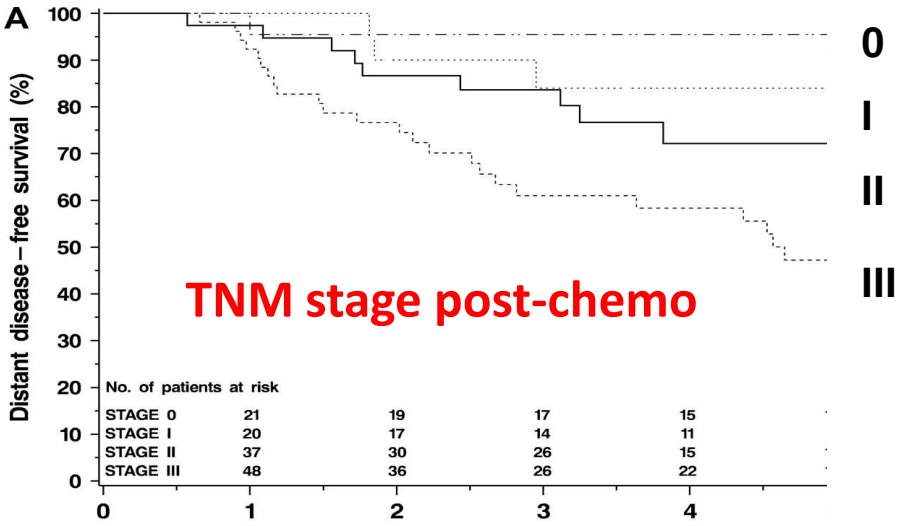
Breast conservation rates higher with preoperative.

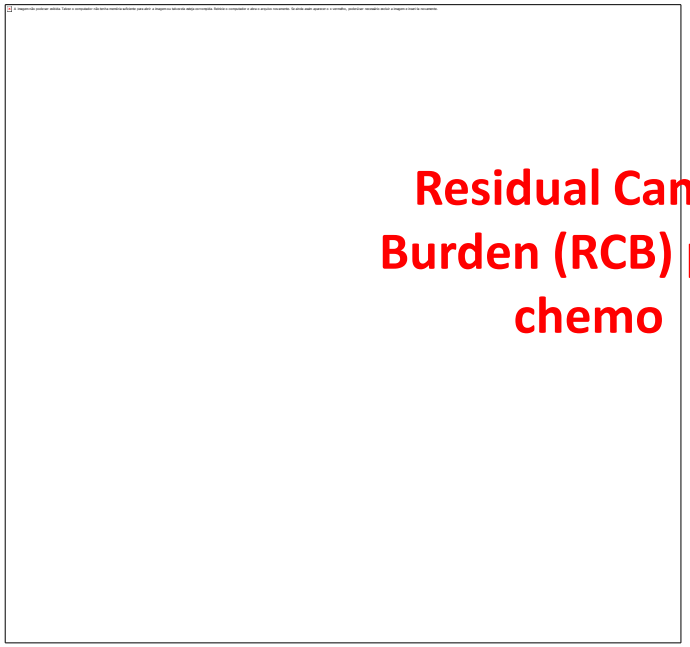
In preoperative therapy you can “see” what’s happening.

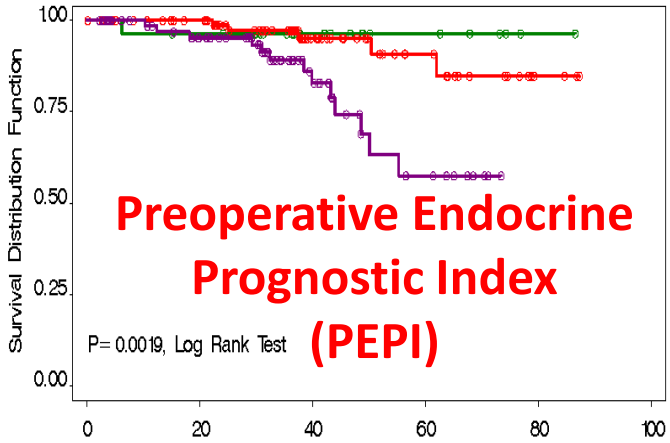
Is that good or bad?

- *Knowledge is power*?
  - Higher BCT rates with preoperative chemotherapy
  - Change regimen in progression
  - Research opportunities!
- *Ignorance is bliss*?
  - Tendency to “churn” through protocols or drugs unless progression
  - Choose endocrine or chemotherapy backbone based on path
  - Is there the temptation to use unproven regimens?
  - Uncertainty in some local management issues

Neoadjuvant Response and Outcome





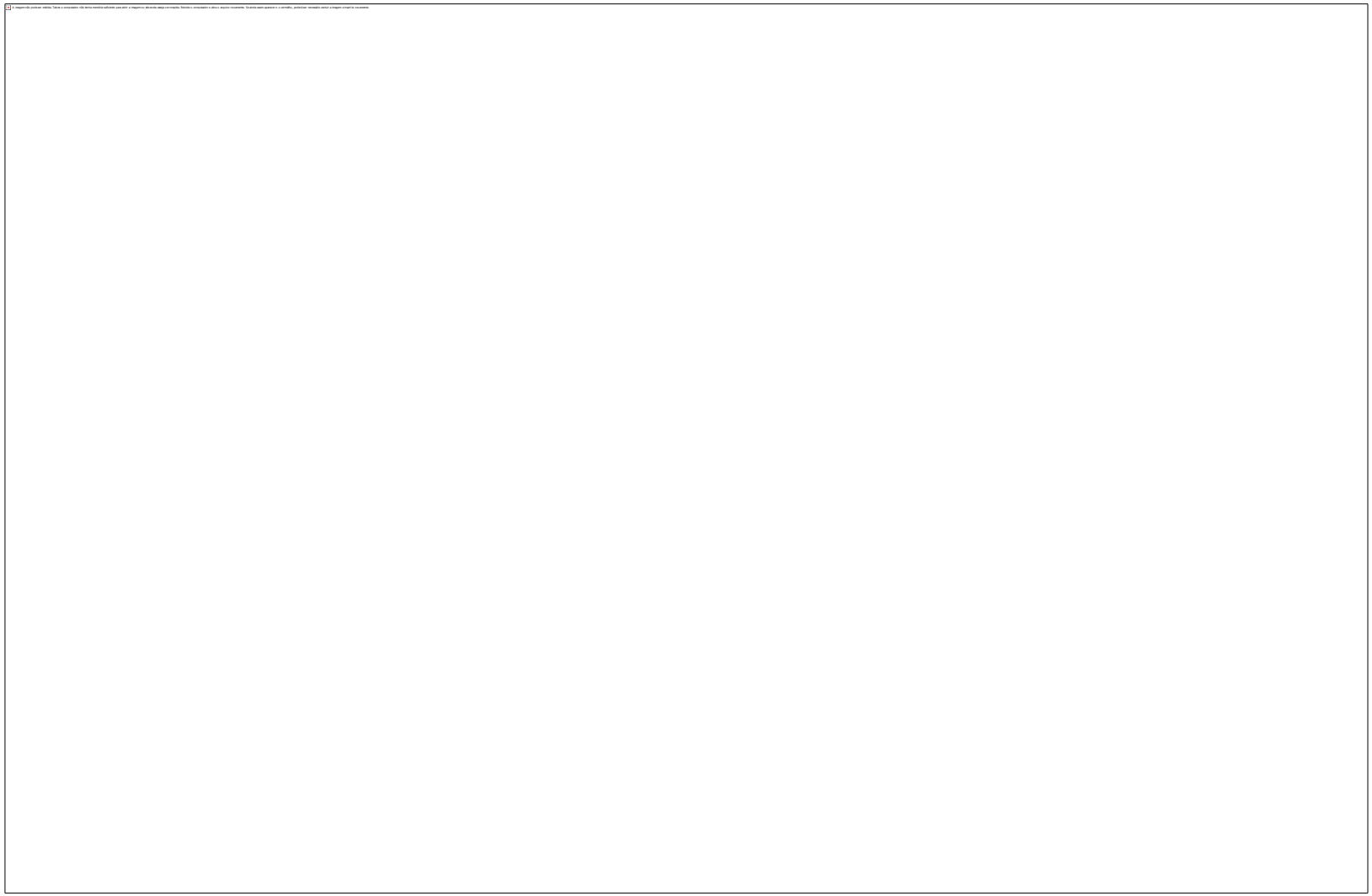


Carey et al, JNCI '05; Symmans et al, JCO '07; Ellis et al, JNCI '08; Ogston, The Breast '03; Rodenhuis et al, Ann Onc '10

Response categorization:

- ***pCR - validated broadly***
- ***RCB = wider prognostic categories***
- ***pCR and RCB0/1 unusual in ER+ HER2-***
  - ***PEPI = T, N, post Rx Ki67 and ER***
- ***Miller-Payne, Neoadjuvant Response Index …***

GEPARquinto

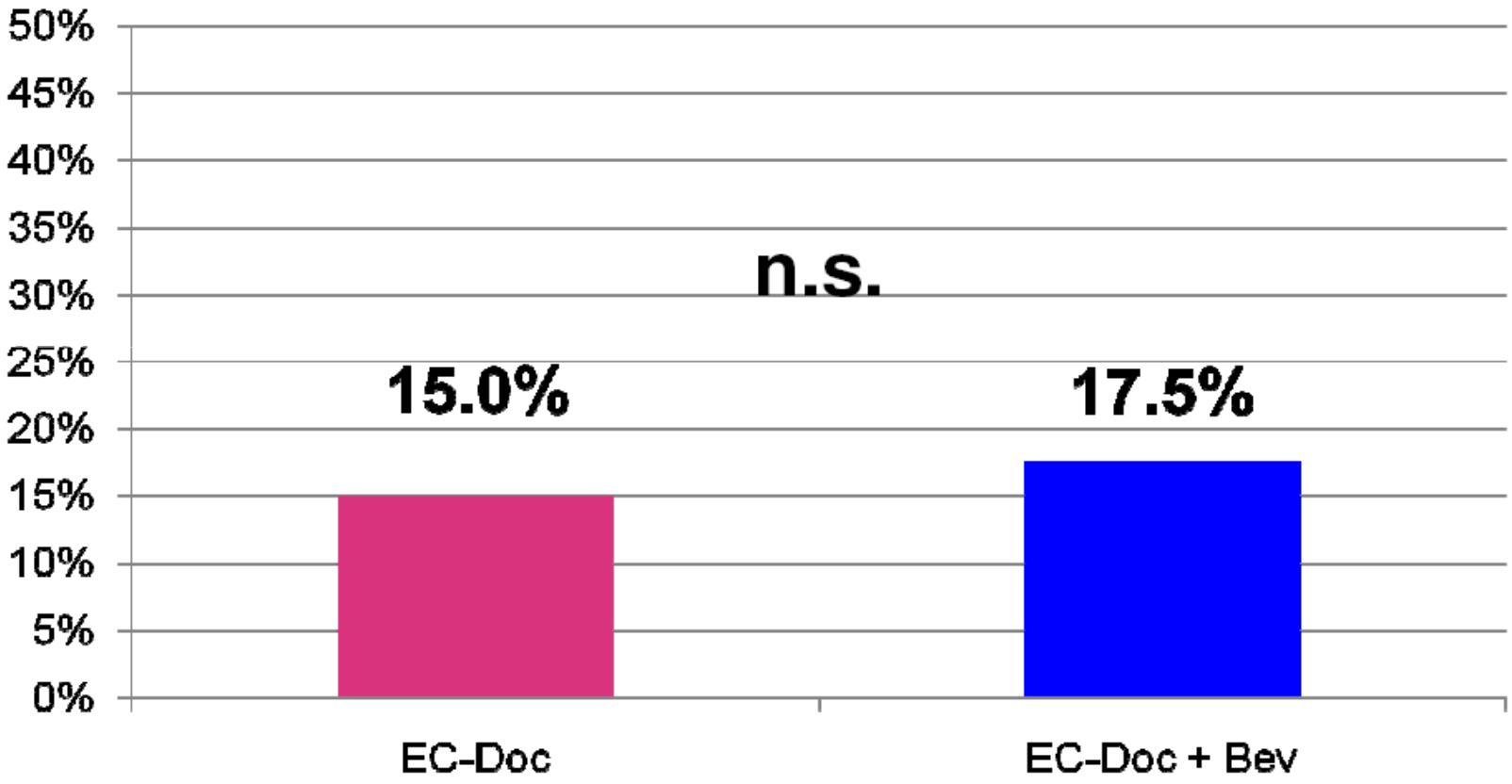


Von Minckwitz et al. SABCS 2010.

GEPAR quinto

pCR

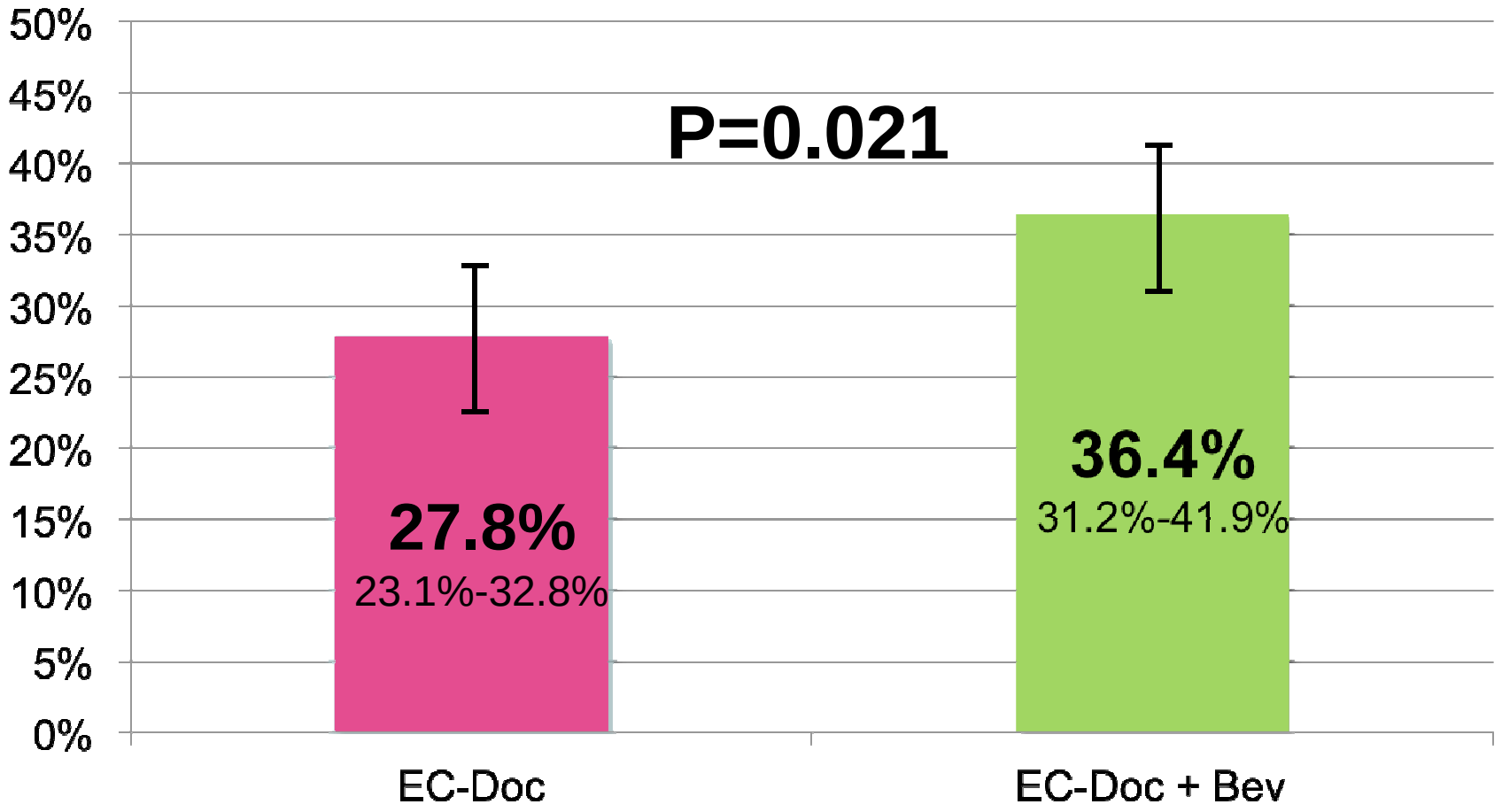
(no invasive/non-invasive residual in breast & nodes based on central pathology report review)



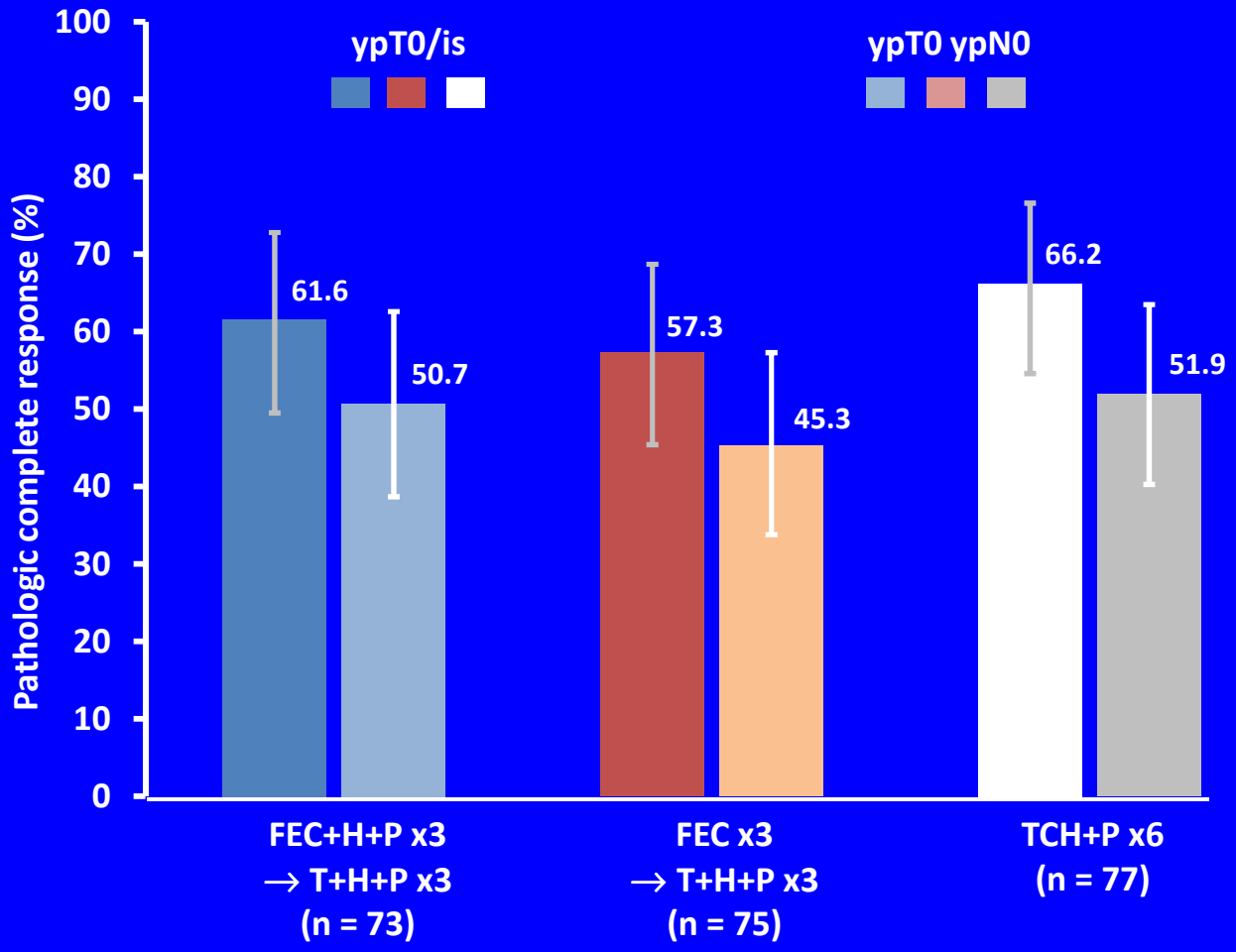
von Minckwitz et al. SABCS 2010; Oral S4-6

pCR within the TNBC subgroup

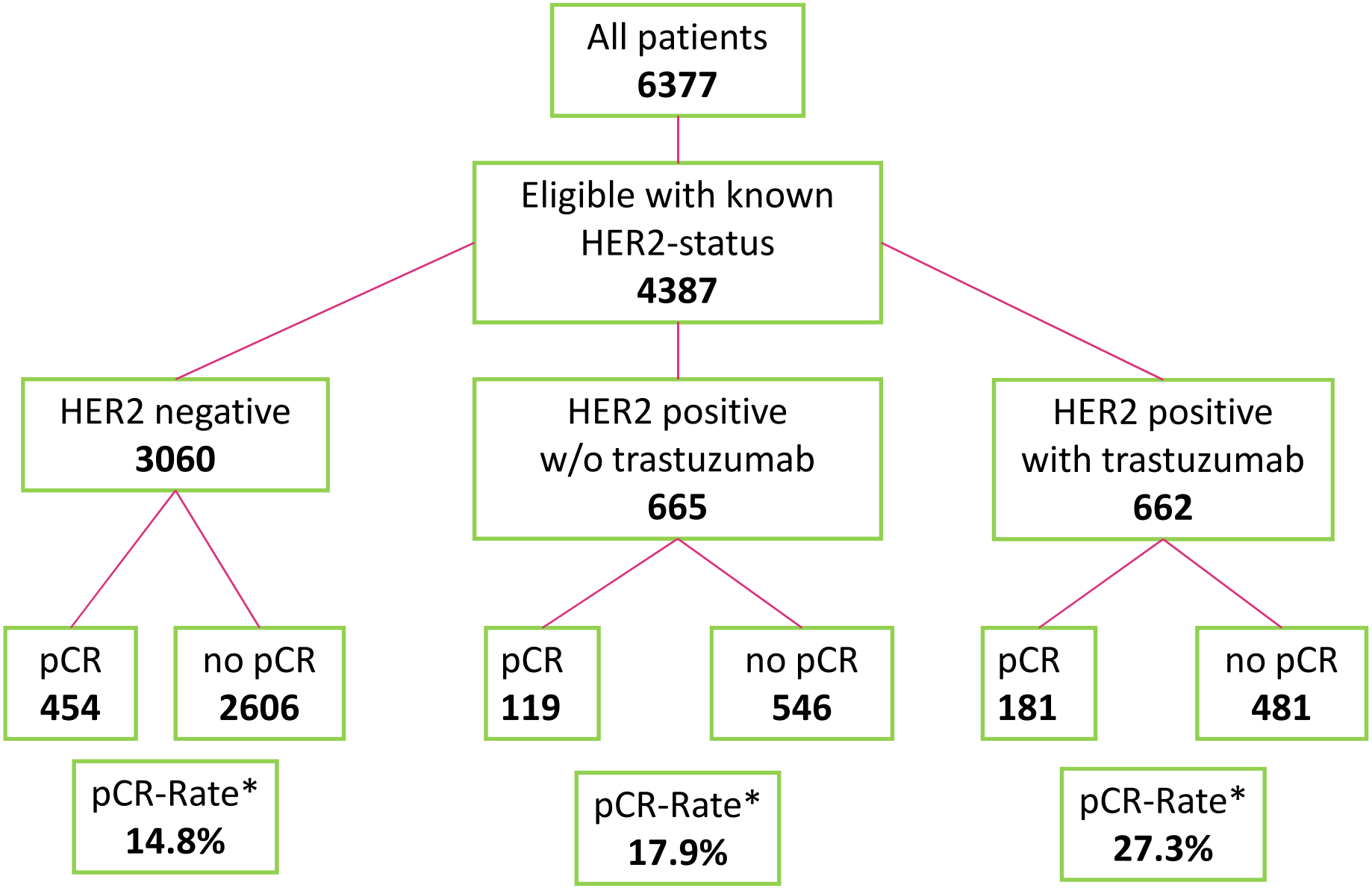
(no invasive/non-invasive residual in breast & nodes
based on central pathology report review n=669)



TRYPHAENA – Neoadjuvant HER2 Pathologic complete response



FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

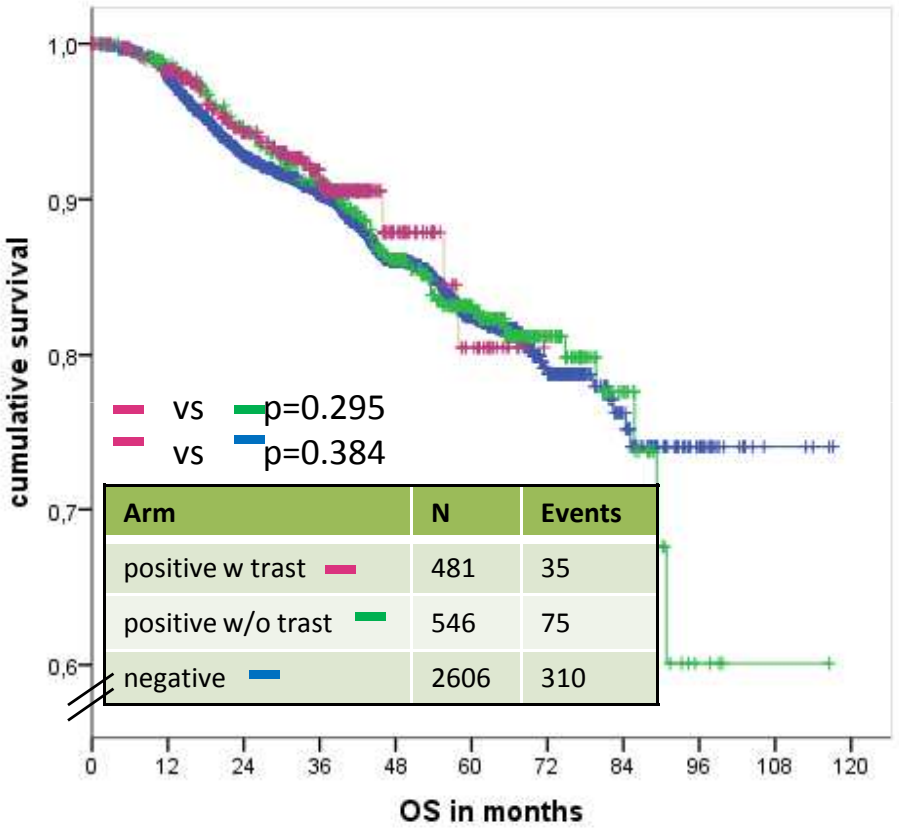


*ypT0 ypN0

Loibl S et al, 2011

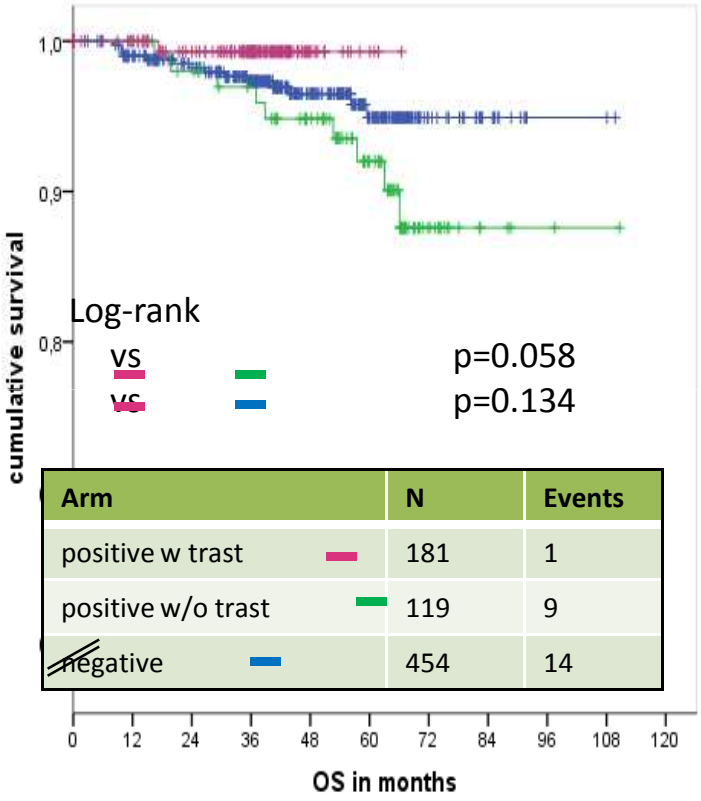
OS analysis by pCR

No pCR



Arm	N	Events
positive w trast	481	35
positive w/o trast	546	75
negative	2606	310

pCR



Arm	N	Events
positive w trast	181	1
positive w/o trast	119	9
negative	454	14

n= 662 HER2+ with trastuzumab
n= 3060 HER2 negative
n= 665 HER2+; no trastuzumab

Loibl S et al 2011

If pCR predicts for OS

- HER2 + have an increased pCR compared with other subtypes with the addition of antiHER2 agents
  - this group may have the advantage of getting systemic therapy earlier with neoadjuvant
  - Combination anti HER2 therapy may increase pCR
  - Introduction of new agents
- TNBC – a heterogeneous group which may or may not have a high pCR with chemo
  - Therefore neoadjuvant therapy may provide a good lab for assessment
  - BUT if not responding early surgery or RT should be considered
  - Opportunity to assess different subtypes of TNBC

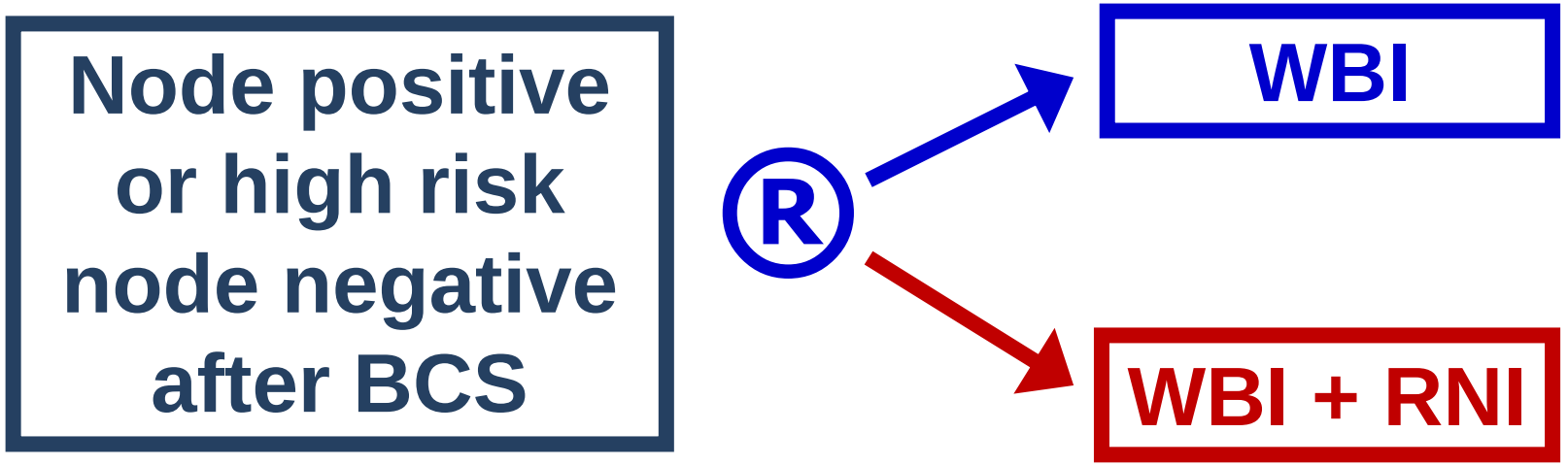
Luminal Subtypes

- pCR rate is poor but is this a group that may benefit from a trial of endocrine therapy
- IF no or poor response is this an indication for chemotherapy?
- Or for other targeted therapy?
- OR with a poor pCR are young endocrine + patients better off treated with surgery and then systemic therapy
- Nodal burden assessment
- Debulking with surgery first? Is B18 a suggestion of this?

Difficulties with Neoadjuvant

- Referral patterns must be set up for neoadjuvant
- Assessment of the axilla needs to be done
- Clips in the primary tumour prior to therapy
- Follow-up and frequent clinical and radiological assessment of the tumor to ensure it is responding
- Rapid intervention if no response
- What do you do if NO pCR
  - No data on what to do when there is bulky residual disease
  - Trials for further treatment

Study Design



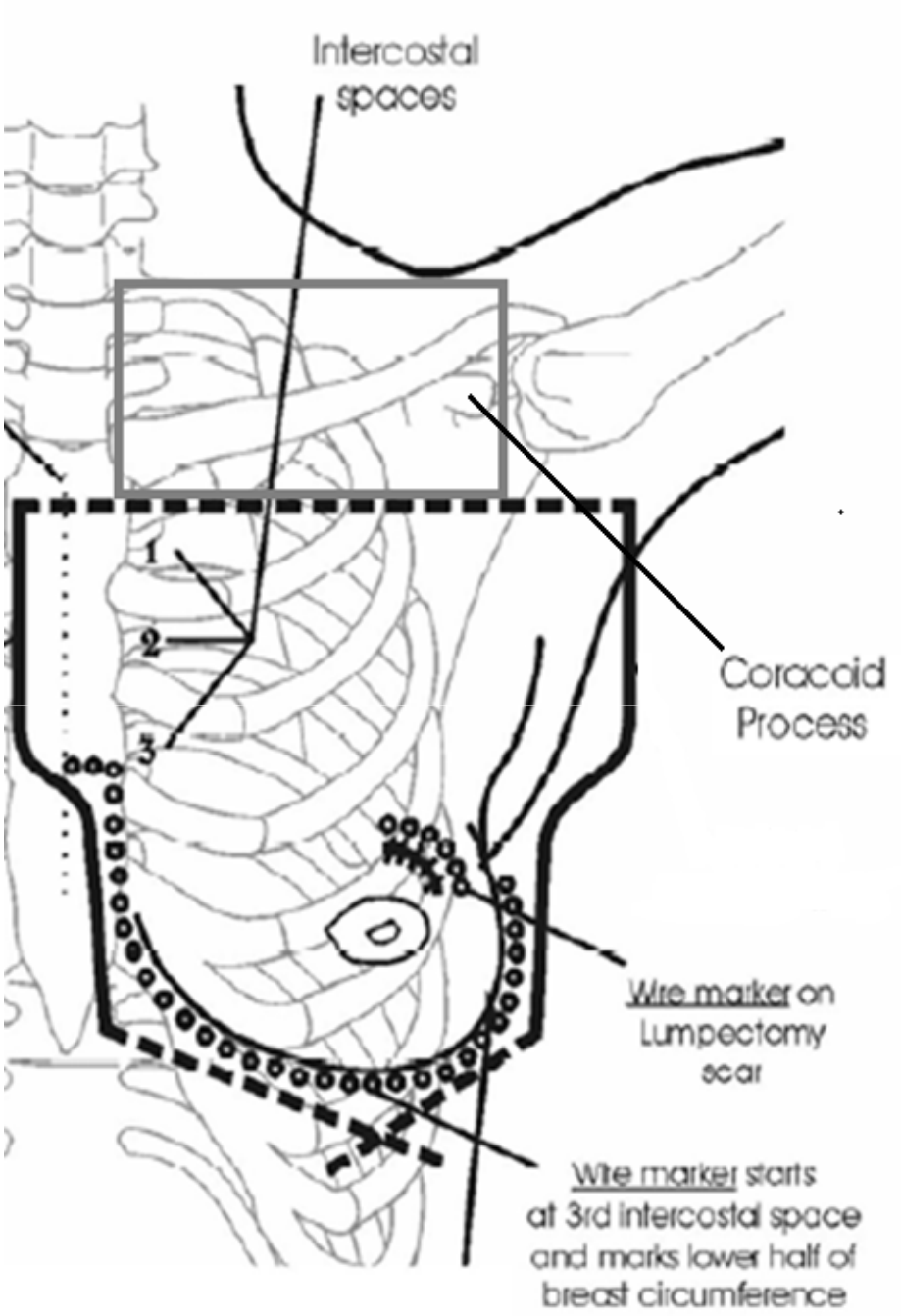
Stratification

- Axillary nodes removed (<10, ≥10)
- Positive axillary nodes (0, 1-3, >3)
- Chemotherapy (anthracycline, other, none)
- Endocrine therapy (yes, no)

Methods

WBI + RNI

- Treat breast + IM, SC and level 3 AX nodes
- IMN volume treated with a modified wide tangent technique or direct field matched to tangent fields
- SC and level 3 AX nodes treated with an anterior field
- Dose to the breast and boost irradiation same
- Dose to the regional nodes: 45 Gy/25 fractions



MA20 Results

Endpoint / Number of pts	916	916
Overall 5y DFS	84%	89.7%
Local Regional 5yDFS	94.5%	96.8%
Distant 5yDFS	87%	92%
Overall Survival	90.7%	92.7%

Other Advantages of Neoadjuvant

- Young women with possible hereditary risk
  - BRCA testing prior to making a surgical decision
- Assessment of tumor response

How Can Neoadjuvant Therapy Accelerate Progress?

- Allow tissue-intensive correlative studies
- Provide proof of principle before moving into more definitive trial
  - defined improvement in pCR leads to adjuvant trial
  - “pick-the-winner” to move into larger trial if multiple apparently equal options exist
- Characterize patients at high risk of recurrence for novel treatments

Neoadjuvant Trial "Labs"

Concept	Neoadjuvant Trial	Predicted Stage IV Trial?	Predicted Adjuvant Trials?
Aromatase inhibitor > tamoxifen in ER+	IMPACT	Y	Y
AC-T > AC alone	NSABP B-27	-	Y
H/chemo > chemo in HER2+	MDACC	Y	Y
HL/chemo > H/chemo in HER2+	NeoALTTO	Y	?
HP/chemo > H/chemo in HER2+	NeoSPHERE	Y	?
Bev/chemo > chemo in TNBC	GeparQuinto	Y/N	?
RAD001/chemo > chemo in TNBC	GeparQuinto	?	?
RAD001/AI > AI in ER+	NCT00107016	Y	?

H=trastuzumab, L=lapatinib, P=pertuzumab, Bev=bevacizumab

Smith et al, JCO'05; Bear et al, JCO '06; Buzdar et al, CCR'07; Baselga et al, SABCS'10; Gianni et al, SABCS'10; von Minckwitz et al, ASCO'11; von Minckwitz et al, SABCS'11; Baselga et al, JCO'09

Summary

- Neoadjuvant therapy requires good coordination of multidisciplinary care and rapid referral patterns
- Separate LABC from neoadjuvant in terms of decision making
- Need to ensure that the subtype is known and that the axilla is assessed for future local therapy
- Some subtypes may benefit more from neoadjuvant therapy
  - HER2 overexpressing
  - TNBC
  - Persons with ? BRCA mutations
  - Elderly with co morbid conditions and ER+ tumours

Summary – Research Advantages

- Neoadjuvant trials have advantages:
  - Smaller, faster trials can guide larger definitive trials
  - Embedded tissue-based studies key to selection strategies
- Triple Negative – ongoing challenge
  - Promising targeted drugs still not clear
  - TNBC ≠ a subtype. BRCA1 ≠ sporadic TNBC.
  - Need to categorize biology to design appropriate trials.
- HER2-targeting – development of new treatments
  - Dual targeting will become norm
  - Limiting chemotherapy is a worthy goal
  - Neoadjuvant trials can choose direction of adjuvant trials