Neoadjuvant Chemotherapy

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Goals of Neoadjuvant Chemotherapy (NACT)

- Reduce the extent of surgery required in breast and axilla
- Use clinical response to therapy as an *in vivo* chemosensitivity assay to guide administration of chemotherapy (CT)
- Improve disease-free survival (DFS) and overall survival (OS) using pathological response rate for selection of subsequent treatment in individual patients
- Serial tissue biopsies for molecular profiling and biological monitoring

NACT (What We Know)

- Established as the standard of care for patients with locally advanced breast cancer
- For operable breast cancer, NACT results in identical outcomes to adjuvant systemic therapy (ACT)
- NACT improves breast conservation results
- There is clear correlation between tumor response in breast and lymph nodes and both DFS and OS
- NACT must be administered as part of a coordinated, multimodality treatment program

Conditions to Employ NACT in Clinical Practice

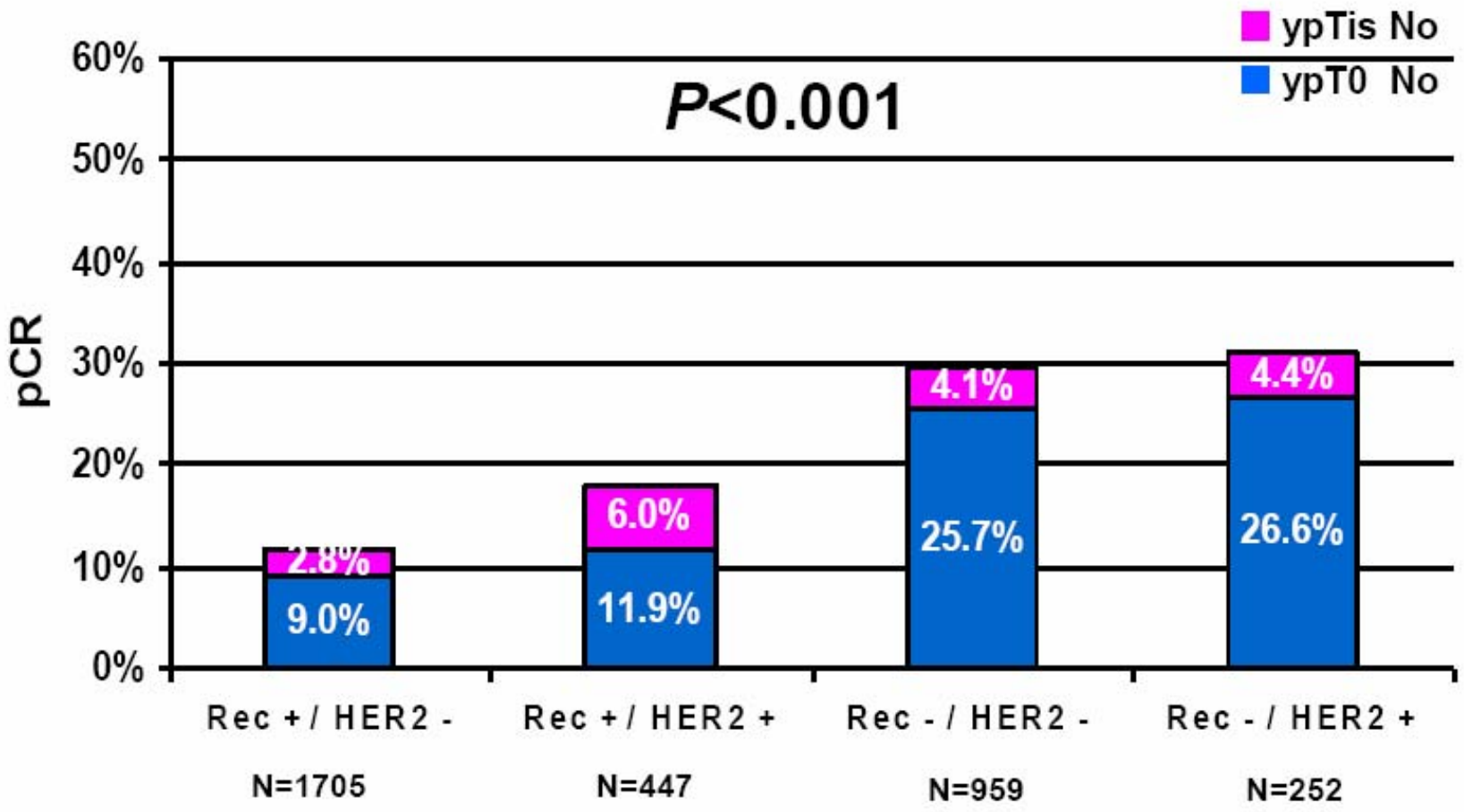
- Opportunity for an application of breast-conserving surgery (BCS)
- In the cases where (postoperative) ACT should be applied

Which Patients Should Be Excluded From Receiving Any NACT?

- When conversion from mastectomy to BCS is impossible?
- CT contraindicated
- Patients not candidates for postoperative CT
  - ER+PgR+ /HER2– ?
  - Elderly ?

Is NACT Less Effective in ER+PgR+ / HER2- Breast Cancer (pCR)

Predictive Factors*
Receptor & HER 2 Status



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* excluding patients treated with trastuzumab or unknown HER2 status

von Minckwitz G, et al. *Cancer Res.* 2009;69(suppl 2): Abstract 79.

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HR Status and NACT Activity

Biomarker	pCR n, %	<pCR n, %	*P* Value
ER status			<.0001
Positive (n = 115)	18 (16%)	97 (84)	
Negative (n = 88)	39 (44%)	49 (56%)	
PR status			<.0001
Positive (n = 95)	11 (12%)	84 (88%)	
Negative (n = 107)	46 (43%)	61 (57%)	

Livasy C, et al. *BCRT.* 2009;69(suppl 2): Abstract 5102.

HR Status and NACT Activity

ER Allred and pCR

pCR	0	2	3	4	5	6	7	8	Total
No	45	2	1	1	1	5	14	55	124
Yes	32	2	2	0	0	4	4	6	50
	77	4	3	1	1	9	18	61	174

P<.0001

PR Allred and pCR

pCR	0	2	3	4	5	6	7	8	Total
No	53	4	4	3	12	4	13	30	122
Yes	37	2	2	2	0	2	3	2	50
	89	6	6	5	12	6	16	32	172

P<.0001

Livasy C, et al. *BCRT.* 2009;69(suppl 2): Abstract 5102.

Tumor Subtype and HER2 Status and NACT Activity

	pCR n, %	<pCR n, %	*P* Value
Proxy IHC subtype			<.0001
Luminal A (n = 101)	9 (9%)	92 (91%)	
Luminal B (n = 14)	7 (50%)	7 (50%)	
Basal (n = 53)	21 (40%)	32 (60%)	
HER2 (n = 18)	8 (44%)	10 (56%)	

Livasy C, et al. *BCRT* 2009;69(suppl 2): Abstract 5102.

HR Status and NACT Activity

Likelihood of pN0 According to Main Variables

Variable			Univariate *Odds Ratio (95% CI)	*P*	Multivariate ∫ *Odds Ratio (95% CI)	*P*
ER-	vs	ER+	3.27 (2.10-5.15)	<.001	3.12 (1.61-6.25)	<.001
PGR-	vs	PGR+	2.43 (1.57-3.79)	<.001	1.22 (0.61-2.37)	.57
nIBC	vs	IBC	0.96 (0.59-1.60)	.88	1.07 (0.58-2.04)	.81
cN0	vs	cN1-3	1.63 (0.88-2.97)	.11	1.92 (0.94-3.81)	.07
Age ≥50 yr	vs	<50 yr	1.28 (0.85-1.92)	.24	1.26 (0.79-2.03)	.33
cT <5 cm	vs	≥5 cm	1.25 (0.83-1.88)	.28	1.47 (0.89-2.45)	0.13
Grade III	vs	G I-II	1.97 (1.22-3.19)	.005	‡ –	

* Odds Ratio (OR) for the likelihood of having a pN0 based on logistic regression. OR > 1 or OR < 1 are respectively associated with higher or lower likelihood of pCR.

‡ Grade was not included in multivariate analysis due to too many missing data, although it was not significant when included (OR, 1.32 (0.74-2.33), *P* = .33)

∫ 362 patients evaluable for the analysis due to missing data

Abbreviation: IBC, inflammatory breast cancer

Zambetti M, et al. *Cancer Res.* 2009;69(suppl 2): Abstract 5103.

HR Status and NACT Activity

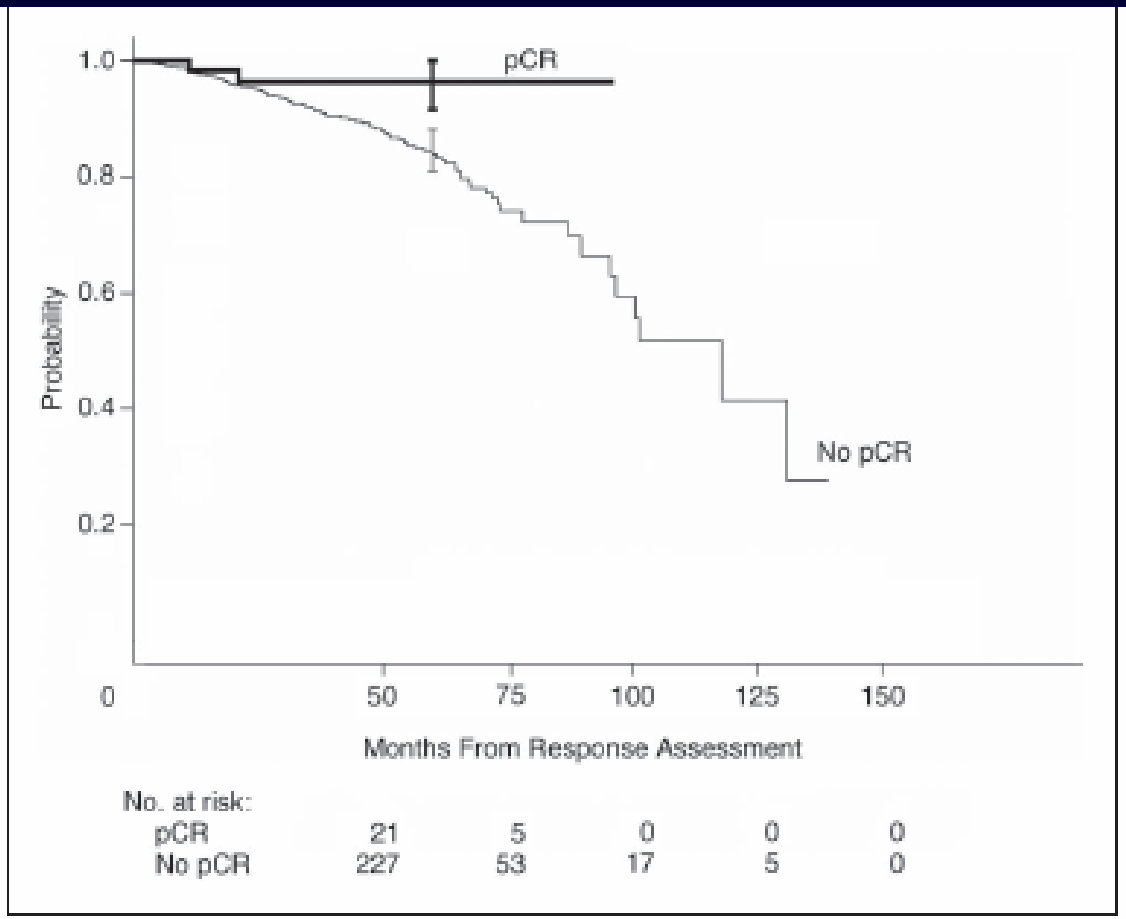
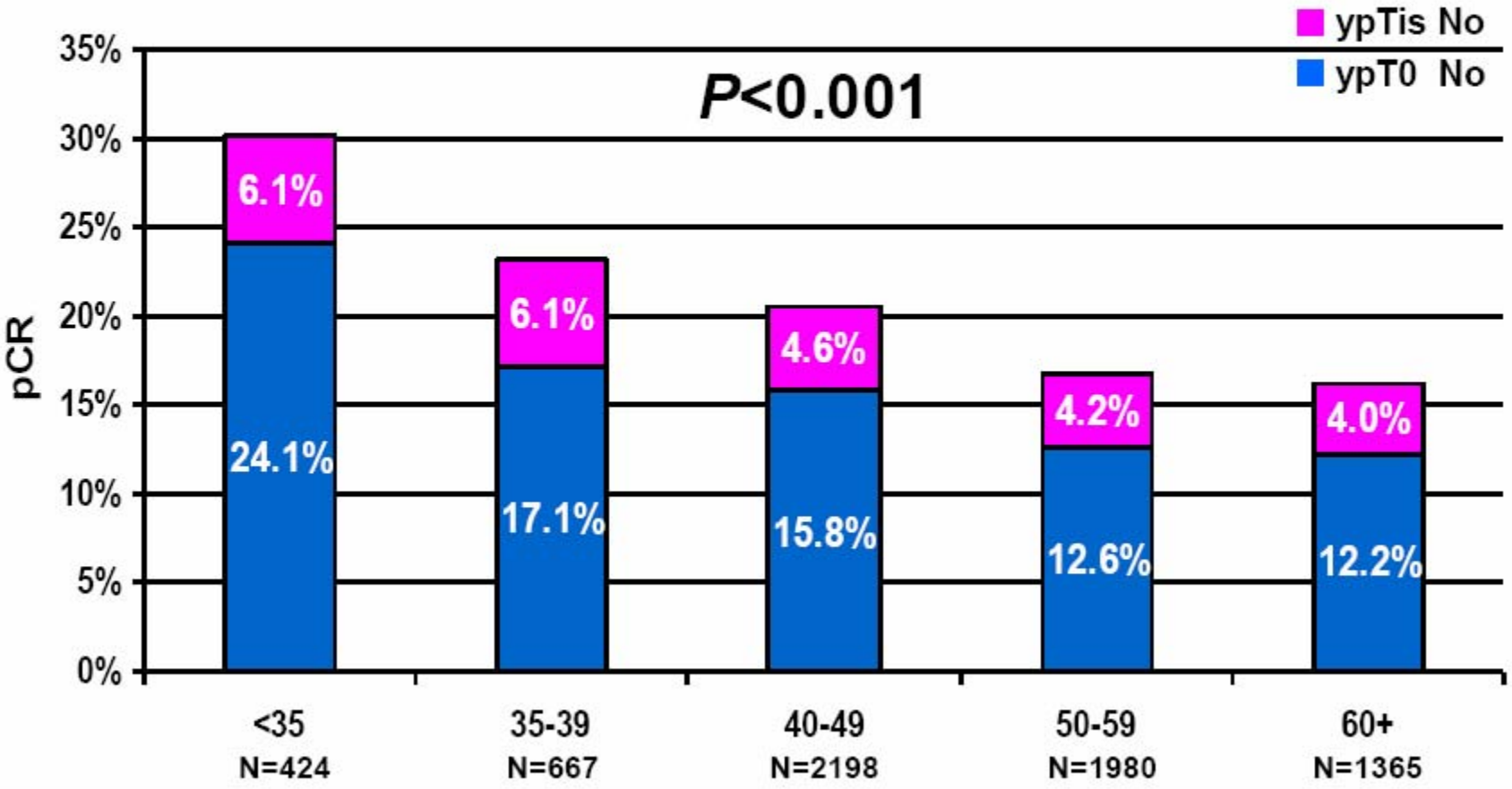


Fig 1. Kaplan-Meier plot of progression-free survival by pathologic complete response (pCR) group (estrogen receptor/progesterone receptor–positive patients).

Guarneri V, et al, *J Clin Oncol.* 2006;24:1037-1044.

Is NACT Less Effective in Older Patients?

Predictive Factors
Age



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von Minckwitz, G et al ***Cancer Res.* 2009;69(suppl 2): Abstract** 79;

Which Early Breast Cancer Patients Do Not Need CT?

Is newer regimens more active in HR+ tumors?

pCR with and without Taxanes

	Without T	With T		Overall
ER -	15%	29%	P < 0.01	20.1%
ER+	2%	8%	p <0.001	4.9%

Mazouni C, *Ann Oncol* 2007

Is (Newer) CT Contraindicated in Older Patients?

Toxicity in GEPARDUO (AC-DOC)

- Median age 51 (24-74)
- FN in 3.4%
- Grade 3-4 neutropenia in 66%
- Grade 3-4 fatigue in 22%
- Grade 3-4 vomiting in 22%
- Grade 3-4 stomatitis in 8%
- Grade 3-4 diarhoea in 4%

von Minckwitz G, JCO 2005

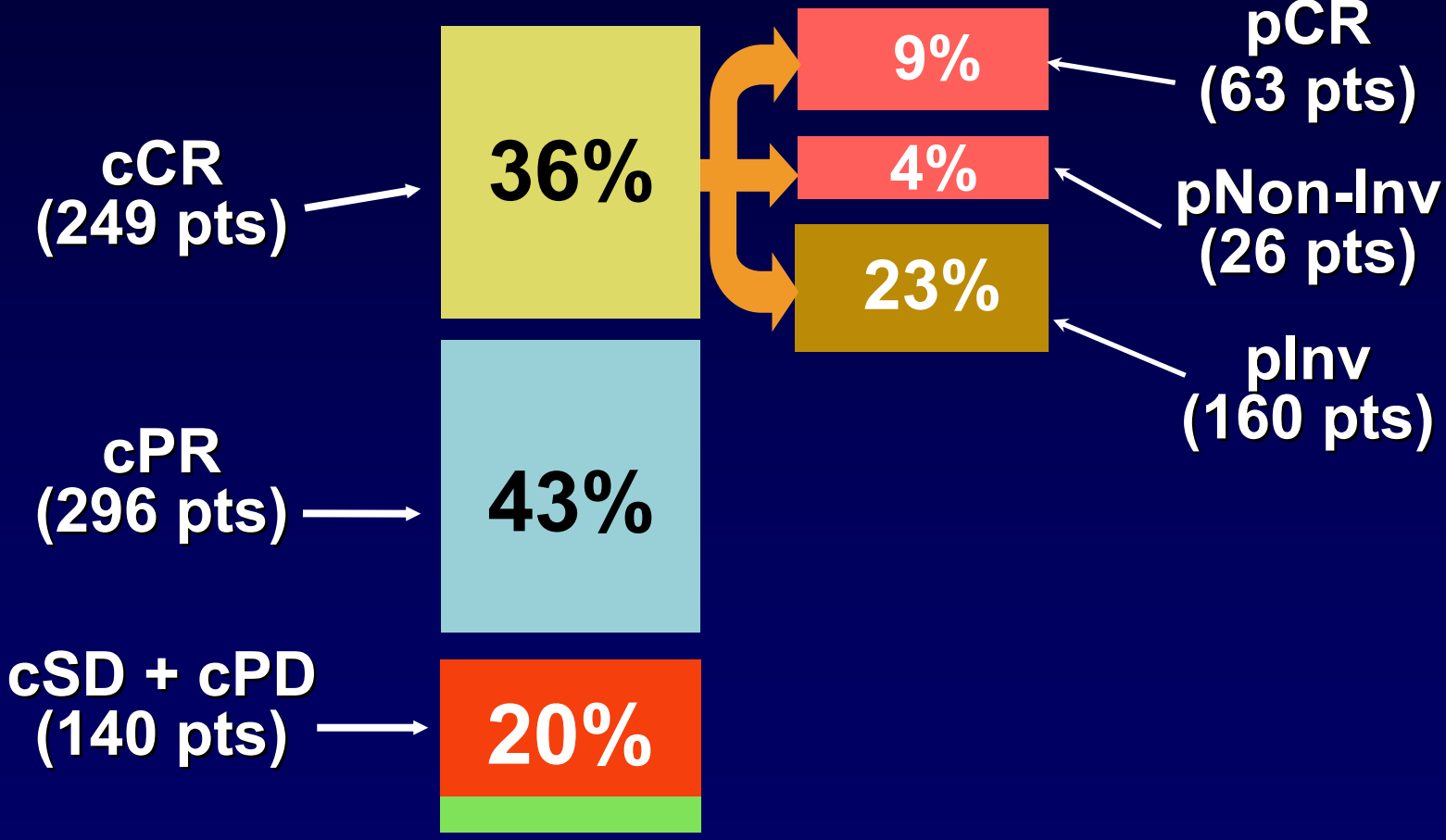
Is a NACT Reasonable in This Patient?

Tumor Reduction After NACT for Primary Breast Cancer

- Tumor palpable
  - Before NACT: 96%
  - After NACT: 45%
- Median Tumor size
  - Before NACT: 4 cm (1.1-9.0)
  - After NACT: 1 cm (0.0-4.5)
- Pathological Complete response: 22%
- Eradication of LN metastases: 28%

Kuerer HM, *Am J Surg.* 2001;182(6):601-608.

NSABP B-18
Clinical and Pathologic Breast Tumor Response to Preop Chemo (685 Patients)



Fisher B, et al. *J Clin Oncol.* 1998;16(8):2672-2685.

BCS in GEPARDUO

	BCS	p univariate	p multivariate
cT < 40 mm	79.3%		
cT > 40 mm	63.8%	0.0001	0.0001
cN0	76.9%		
cN >0	70.0%	0.0001	0.0001
ER+	73.6%		
ER-	80%	0.028	0.047

Loibl I, *Ann Surg Oncol* 2006

Individual Predictive Markers

- There is no individual pathological or molecular marker that can reliably predict response to PCT in an individual patient
- It could be hypothesized that patients with ER-negative, high-grade tumors with high S-phase fraction (or Ki-67) would be more likely to respond than tumors with the opposite characteristics

Selection of Optimal NACT

- **ER and/or PR-positive, HER2-negative:**
  - **Primary endocrine therapy if chemotherapy is contraindicated or tumor is strongly ER/PR positive**
  - **Patients who would receive only adjuvant endocrine therapy are good candidates for primary endocrine therapy**
  - **Identification of tumors that will not respond to chemotherapy is a high priority**
  - **Until then, primary chemotherapy before surgery followed by optimal endocrine therapy after surgery seems to be the optimal strategy**