

Locally Advanced Primary Breast Cancer

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Natural History of Disease

- Most cases of stage III breast cancer were once stage I breast cancer
- In poor countries, more than half of patients have locally advanced or metastatic disease at the time of diagnosis
 - Lack of education
 - Lack of screening

Clinical Presentation

- “Grave clinical signs”
 - Skin ulceration
 - Skin edema
 - Tumor fixation to the chest wall
 - Axillary nodes larger than 2.5 cm
 - Fixed axillary nodes
- Satellite skin nodules and infraclavicular, internal mammary, and supraclavicular adenopathy

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Clinical Presentation of Stage III Breast Cancer



Peau d'orange



Large mass, edema, and erythema

Photographs courtesy of Aman Budzar and Henry Kuerer.

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Clinical Presentation of Stage III, Locally Advanced (Inoperable) Disease



Large primary breast cancer



Locally advanced breast cancer

Photographs courtesy of Frankie Holmes and Merrick Ross.

Diagnostic Work-Up

- Distinguish benign from malignant disease
- Distinguish noninvasive from invasive disease
- Obtain pathologic diagnosis before treatment
 - Percutaneous image-guided biopsy (preferred)
 - Core-needle biopsy
 - Fine-needle aspiration
 - Excisional biopsy

TNM Staging System for Advanced Breast Cancer

- T3** Tumor >5 cm
- T4** Invasion of the chest wall or to the skin (inflammatory breast cancer)
 - T4a** Invasion of the chest wall
 - T4b** Edema, thickening of the skin, or ulceration of the skin or surrounding skin nodules
 - T4c** Signs of both T4a and T4b
 - T4d** Inflammatory cancer (breast is red, swollen, and warm)

Greene FL, et al. *AJCC Cancer Staging Manual*, 6th ed, 2002.

TNM Staging System for Advanced Breast Cancer (cont.)

- N2** Involvement of four to nine axillary lymph nodes or of internal mammary lymph nodes without axillary node involvement
 - N2a** Involvement of four to nine axillary lymph nodes
 - N2b** Involvement of only internal mammary lymph nodes

TNM Staging System for Advanced Breast Cancer (cont.)

- N3** Involvement of 10 or more axillary lymph nodes or of the infraclavicular lymph nodes or of the internal mammary nodes with axillary node involvement
- N3a** Involvement of 10 or more axillary lymph nodes or of the infraclavicular lymph nodes
- N3b** Involvement of the internal mammary nodes and axillary nodes
- N3c** Involvement of the supraclavicular nodes

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Stage Classifications for Locally Advanced Breast Cancer

Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

Singletary SE, et al. *J Clin Oncol.* 2002;20:3576-3577.

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Stage Classifications for Locally Advanced Breast Cancer (cont.)

Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Survival According to Treatment

Treatment	No. of Patients	5-Yr. Survival (%)
Surgery only	2,453	36
Radiation only	2,386	29
Surgery plus radiation	4,249	33
Chemotherapy, surgery, and radiation	1,923	63

Giordano SH. *Oncologist*. 2003;8:521-530.

Systemic Therapy for Breast Cancer

- Goals
 - Attain cure, prevent recurrence, eradicate micrometastases
- Appropriate treatments
 - Tamoxifen or aromatase inhibitors for postmenopausal women
 - Ovarian ablation
 - Chemotherapy
 - Monoclonal antibody therapy
 - Supportive care

Chemotherapy for Breast Cancer

- Improves disease-free and overall survival
- Durations of more than six months do not add major advantage
- Anthracycline-based combinations are better than combination of cyclophosphamide, methotrexate, and fluorauracil (CMF)
- Taxane-based combinations are more effective in the adjuvant setting
- Trastuzumab in the adjuvant setting improves disease-free and overall survival

Neoadjuvant Chemotherapy

- Concept developed concurrently with adjuvant chemotherapy in the 1970s
- Treatment for locally advanced breast cancer (stage III disease)
- Allows for immediate assessment of tumor response
- Allows for the evaluation of new and novel agents

Neoadjuvant Chemotherapy (cont.)

- Goals
 - Decrease tumor size
 - Minimize surgery
 - Establish tumor sensitivity
- Appropriate treatments
 - Chemotherapy
 - Tamoxifen or aromatase inhibitors
 - Radiation therapy

Clinical Rationale for Preoperative Chemotherapy

- Excellent response rates for locally advanced breast cancer
- Efficacy of adjuvant chemotherapy for node-negative breast cancer
- Equivalent survival for breast-conserving surgery and mastectomy

Advantages of Neoadjuvant Chemotherapy

- Increased rate of breast-conserving surgery
- Earlier treatment of micrometastases
- Treatment serves as in vivo chemosensitivity assay
- Improved rates of local control and disease-free survival

Factors Influencing Decision to Use Neoadjuvant Chemotherapy in Operable Breast Cancer

- Does the patient need adjuvant chemotherapy based on information known prior to surgery?
- Would neoadjuvant chemotherapy potentially alter the extent of resection?
- Does the patient desire breast preservation?
- Would treatment benefit from knowledge of in vivo chemosensitivity?

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NSABP B-18 Trial: Schema

Operable Breast Cancer

Stratification

- Age
- Clinical tumor size
- Clinical node status

Operation

AC x 4

+ TAM if ≥ 50 yrs.

AC x 4

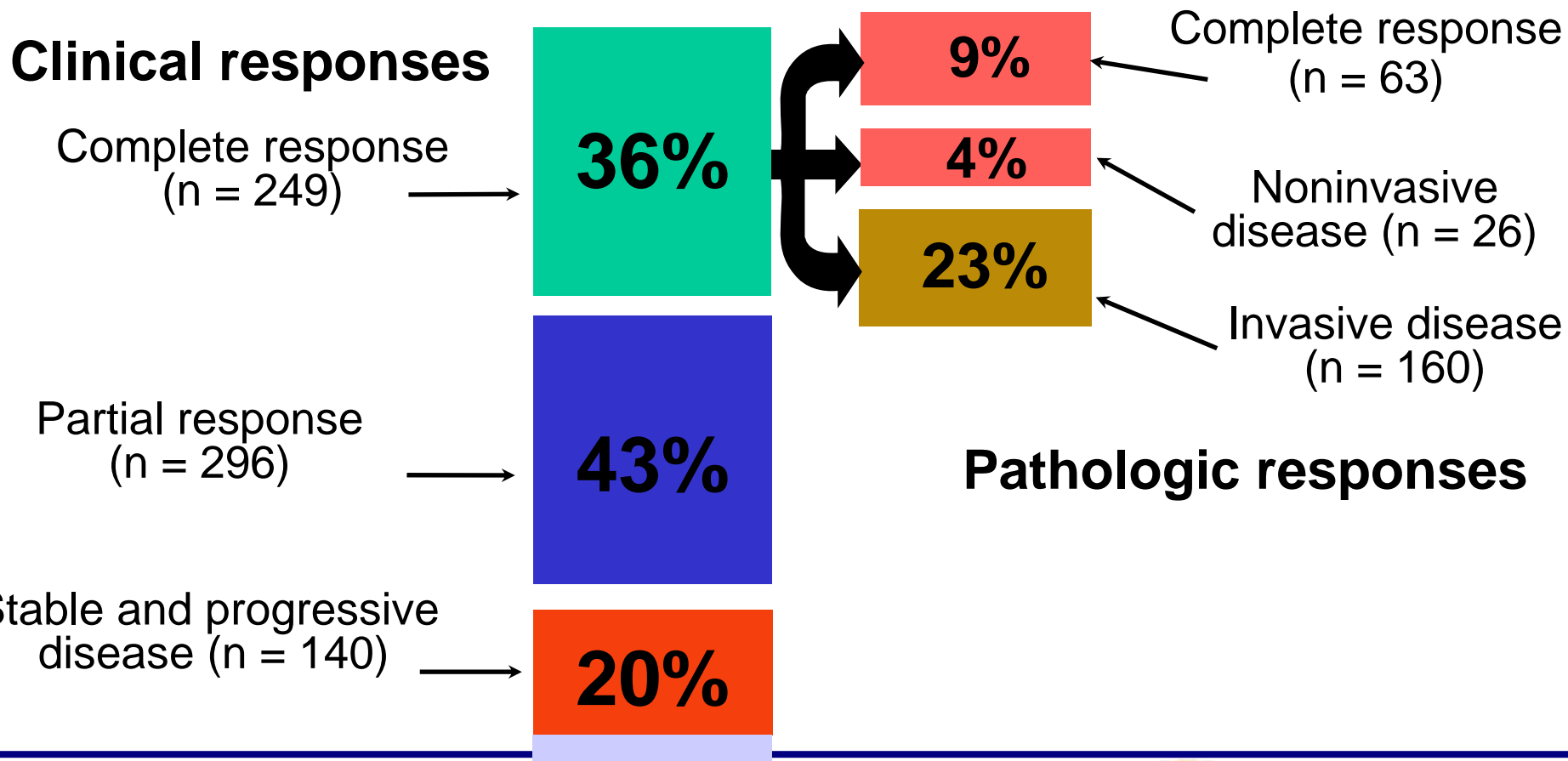
+ TAM if ≥ 50 yrs.

Operation

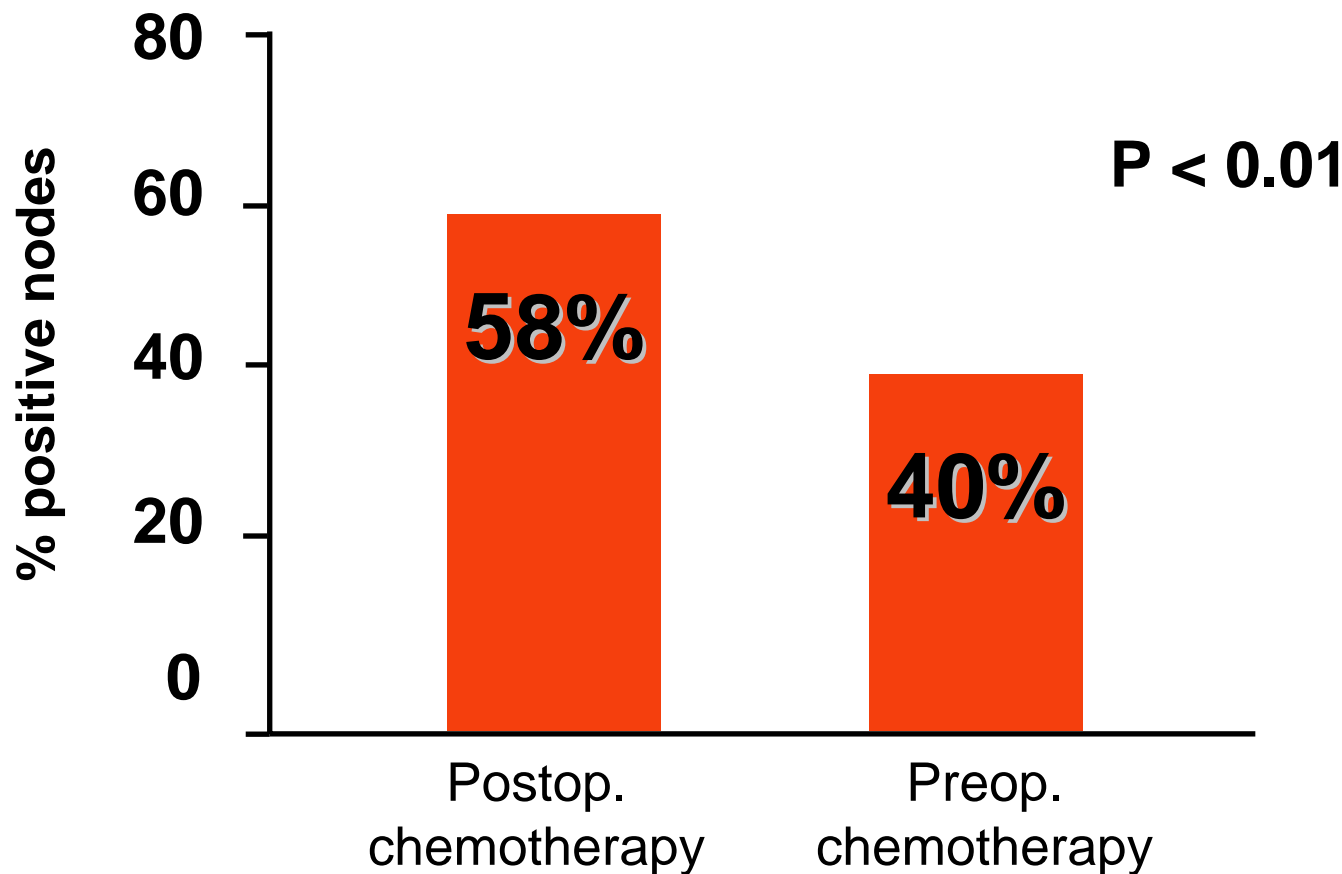
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NSABP B-18 Trial (cont.)

Response to Preoperative Chemotherapy

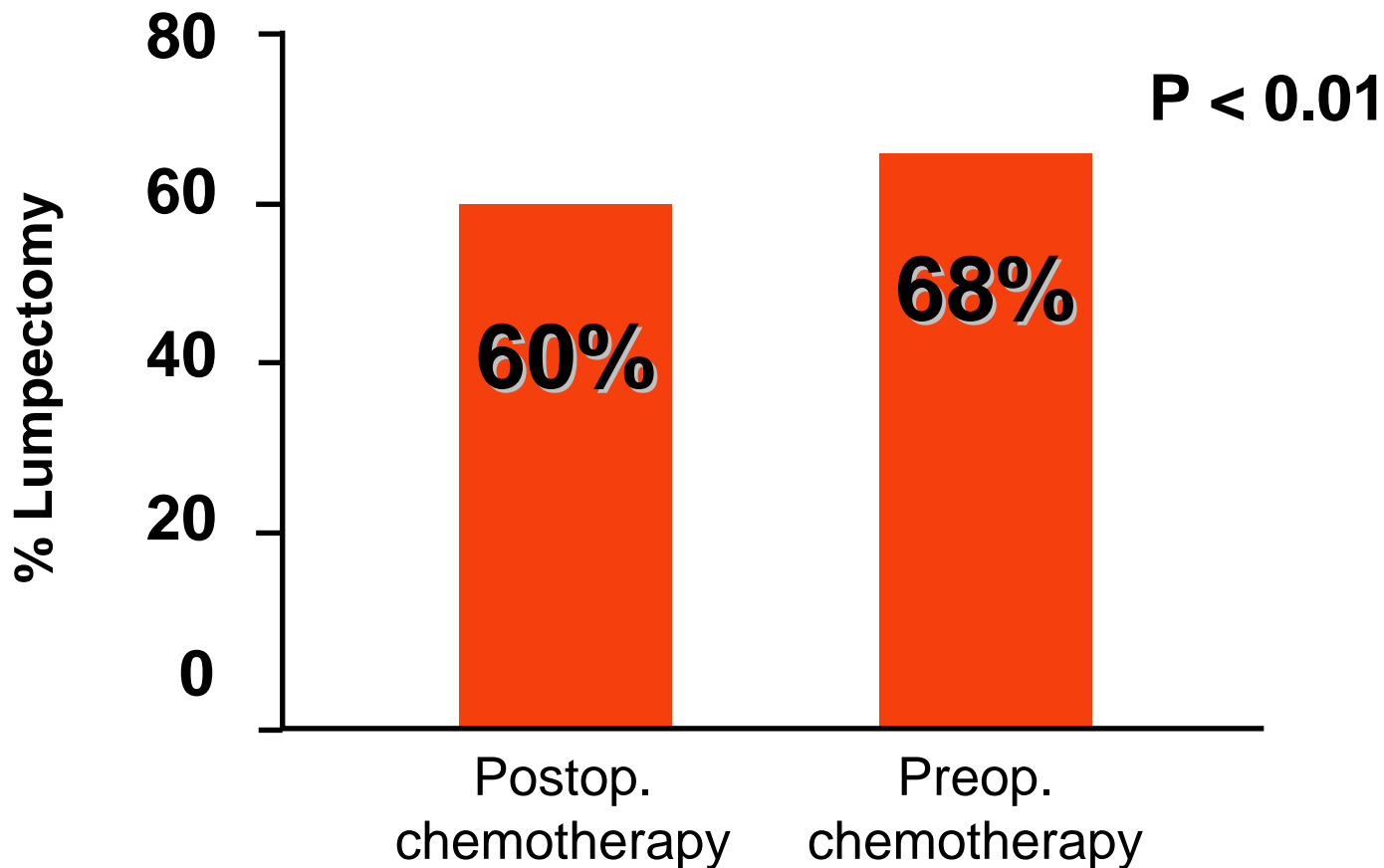


NSABP B-18 Trial (cont.) Pathologically Positive Nodes



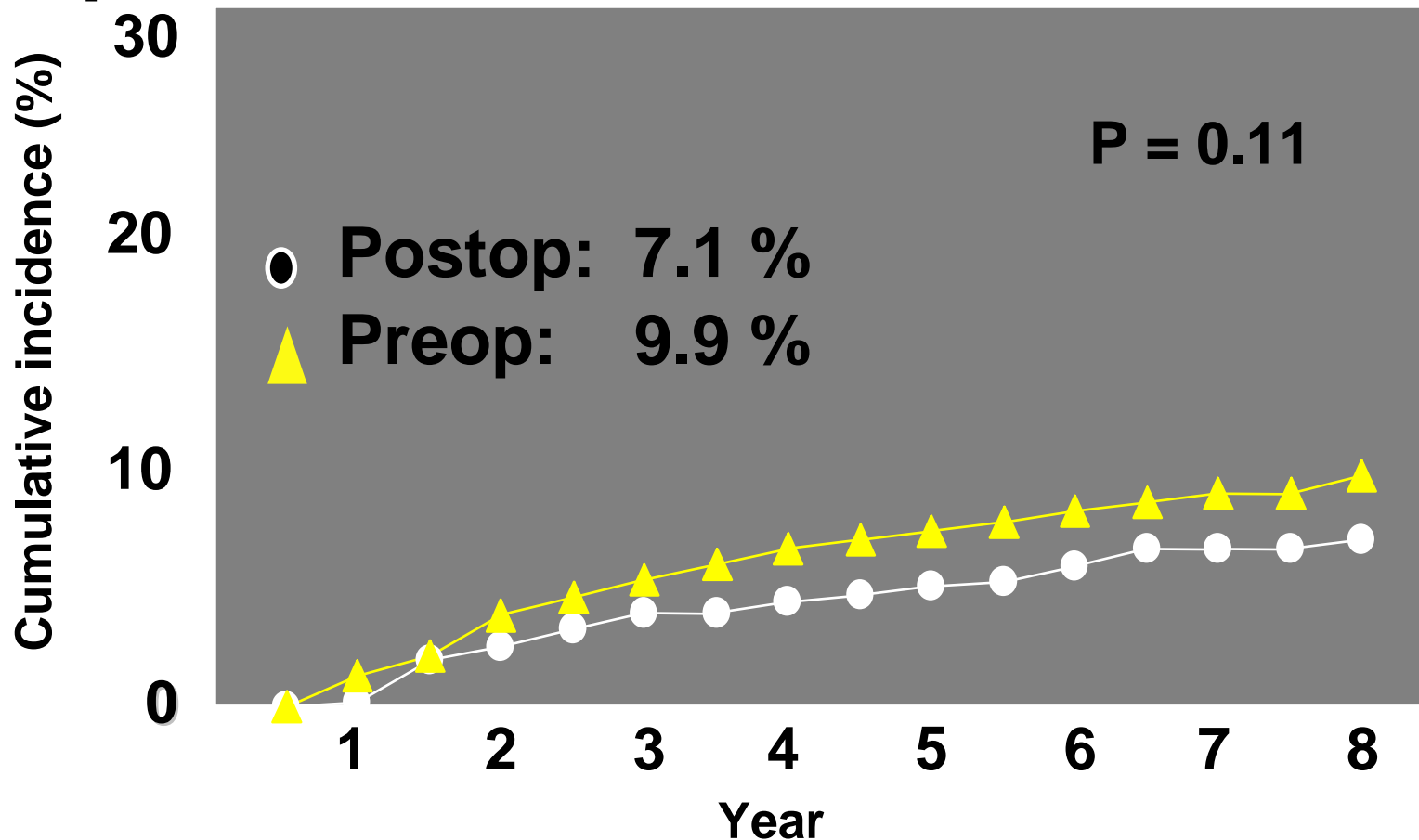
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NSABP B-18 Trial (cont.) Rate of Lumpectomy



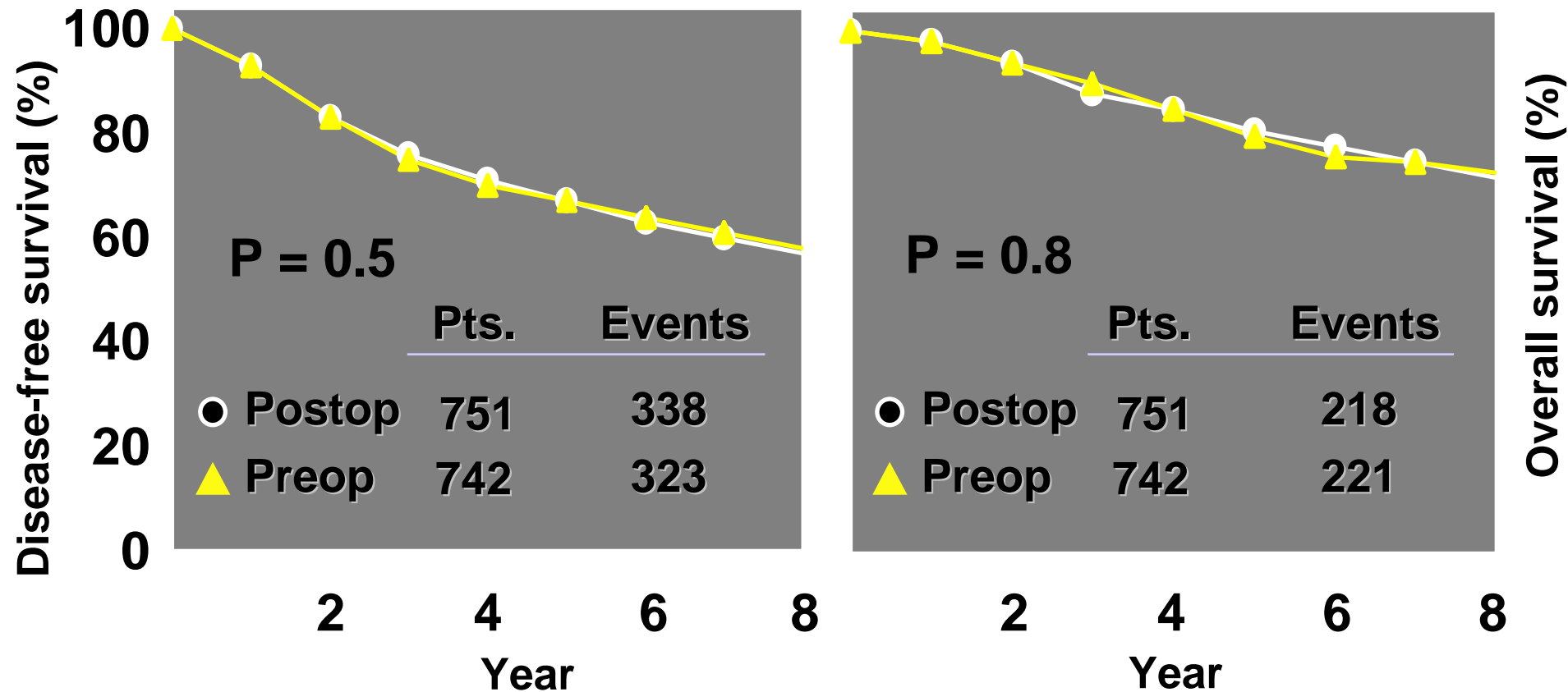
NSABP B-18 Trial (cont.)

Ipsilateral Breast Cancer Recurrence



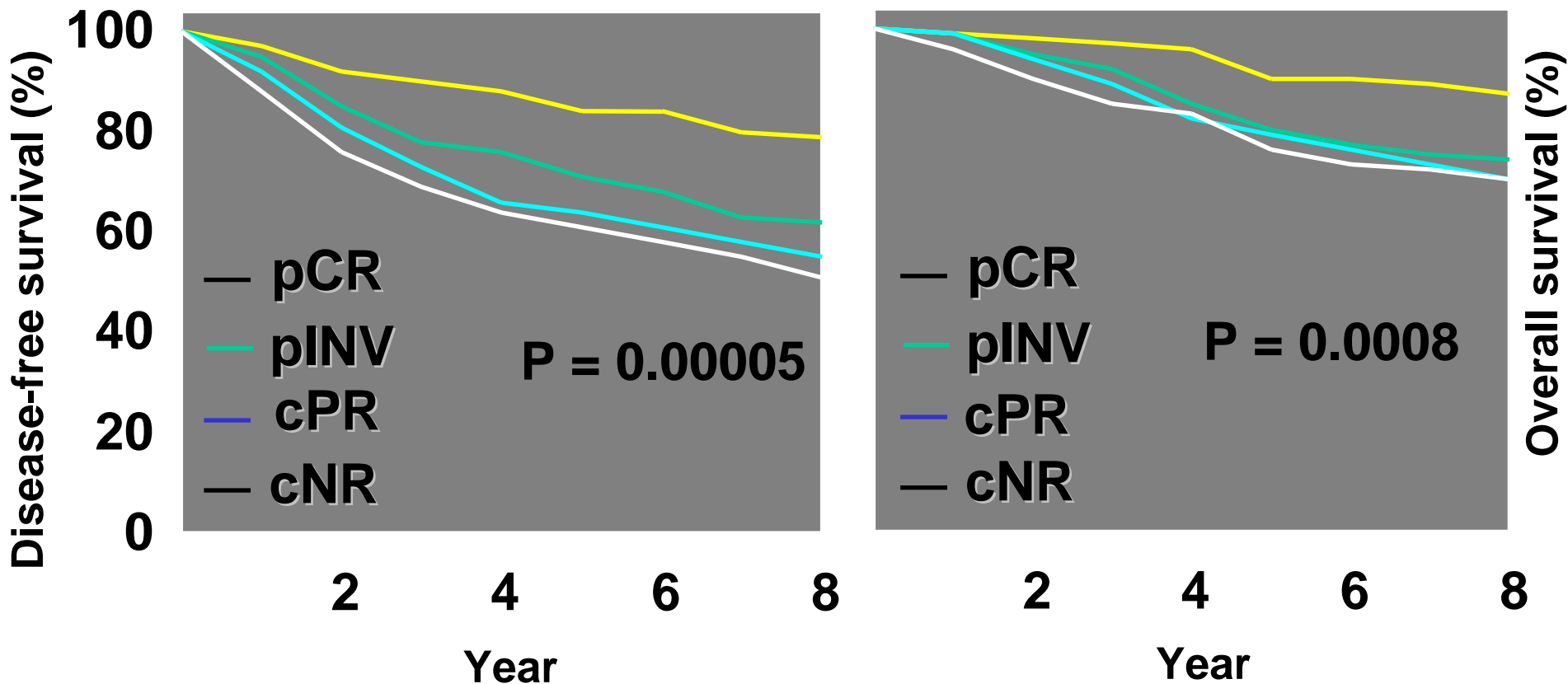
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NSABP B-18 Trial (cont.) Survival



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NSABP B-18 Trial (cont.) Survival According to Response

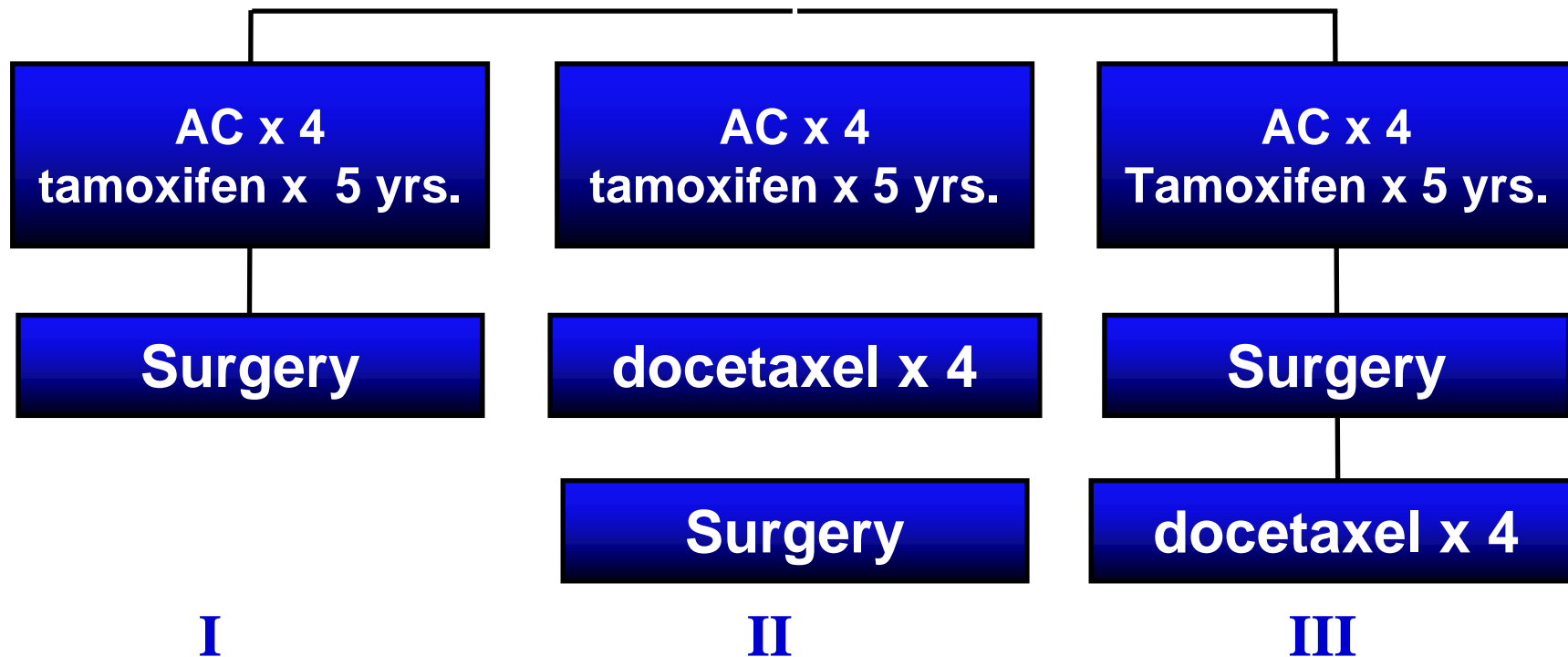


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NSABP B-27 Trial: Schema

Operable Breast Cancer

Randomization



NSABP B-27 Trial (cont.) Effect of Preoperative Docetaxel

Compared with chemotherapy and surgery alone, chemotherapy and docetaxel followed by surgery led to increased rates of

- Clinical response
- Pathologic response
- Downstaging of node disease
- Lumpectomies

NSABP B-27 Trial (cont.) Effect of Postoperative Docetaxel

Compared with chemotherapy and surgery alone, chemotherapy and surgery followed by docetaxel led to increased rates of disease-free and overall survival in subgroups of patients (according to nodes)

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NSABP B-27 Trial (cont.)

Eligibility: Operable Breast Cancer

- Diagnosis by fine-needle aspiration or core biopsy
- Palpable on physical examination
(T1c-3 N 0, M 0 / T 1-3, N 1, M 0)
- Movable in relation to chest wall and skin
- Nodes of any size but not fixed to each other or to adjacent structures
- No arm edema

NSABP B-27 Trial (cont.) Clinical Tumor Size at Entry

Size of Tumor (cm)	Preop. AC (% of Pts.)	Preop. AC + Preop. Docetaxel (% of Pts.)	Preop. AC + Postop. Docetaxel (% of Pts.)
≤2.0	15	15	14
2.1-4.0	40	40	41
≥4.0	45	45	45

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NSABP B-27 Trial (cont.) Clinical Node Status at Entry

Node Status	Preop. AC (% of Pts.)	Preop. AC + Preop. Docetaxel (% of Pts.)	Preop. AC + Postop. Docetaxel (% of Pts.)
Negative	70	70	69
Positive	30	30	31

NSABP B-27 Trial (cont.) Grade of Tumor at Entry

Tumor Grade	Preop. AC (n = 2,400)	Preop. or Postop. Docetaxel (n = 1,494)
1	22	15
2	50	40
3	13	16
4	10	24

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NSABP B-27 Trial (cont.) Treatment Regimen

Chemotherapy: doxorubicin, 60 mg/m²
cyclophosphamide, 600 mg/m²

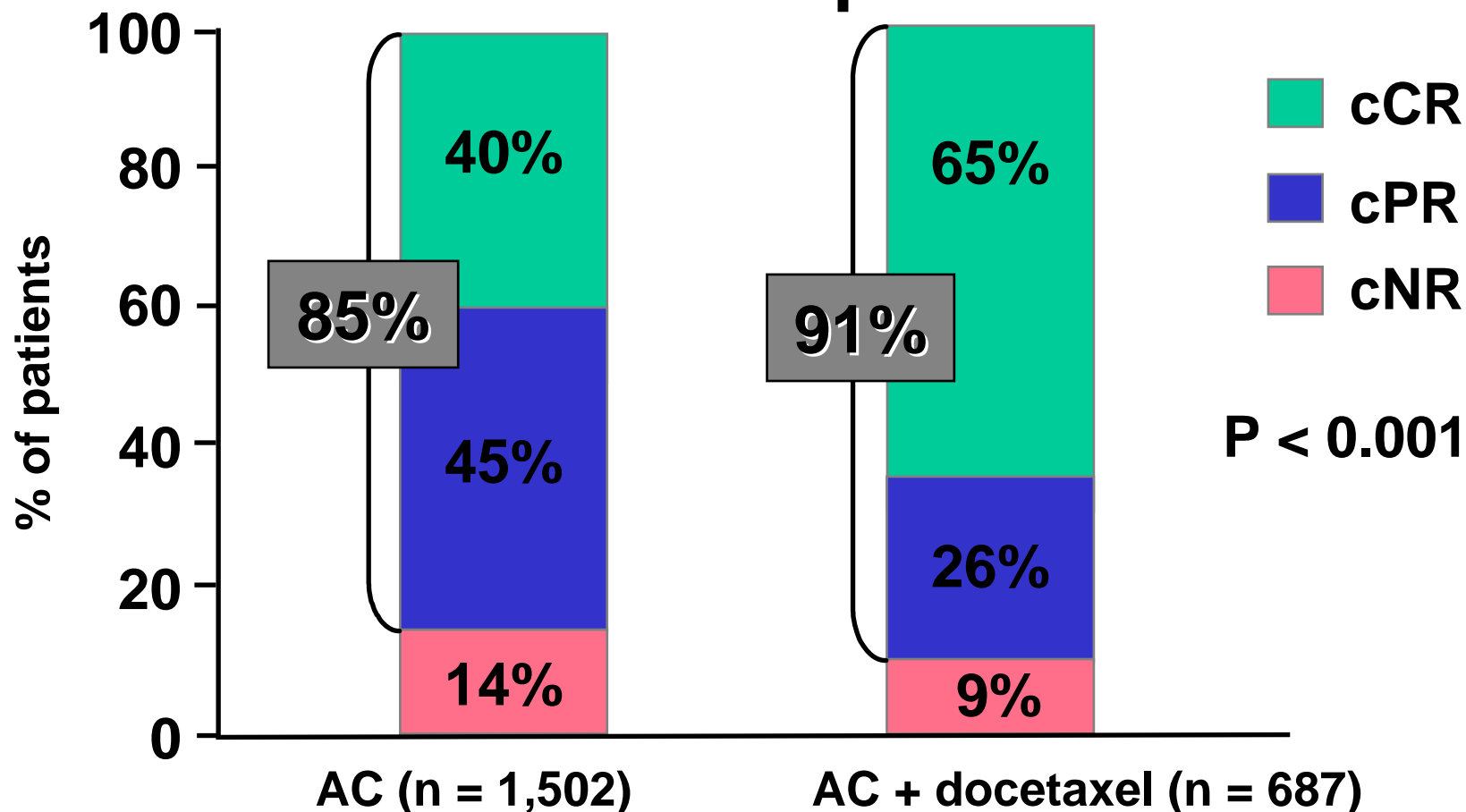
Docetaxel: 100 mg/m²

Tamoxifen: 20 mg, orally, daily for five years
(beginning on day 1 of chemotherapy)

Radiation: Only for patients who had lumpectomy;
done after surgery (arms I and II) and after
treatment with docetaxel) (arm III)

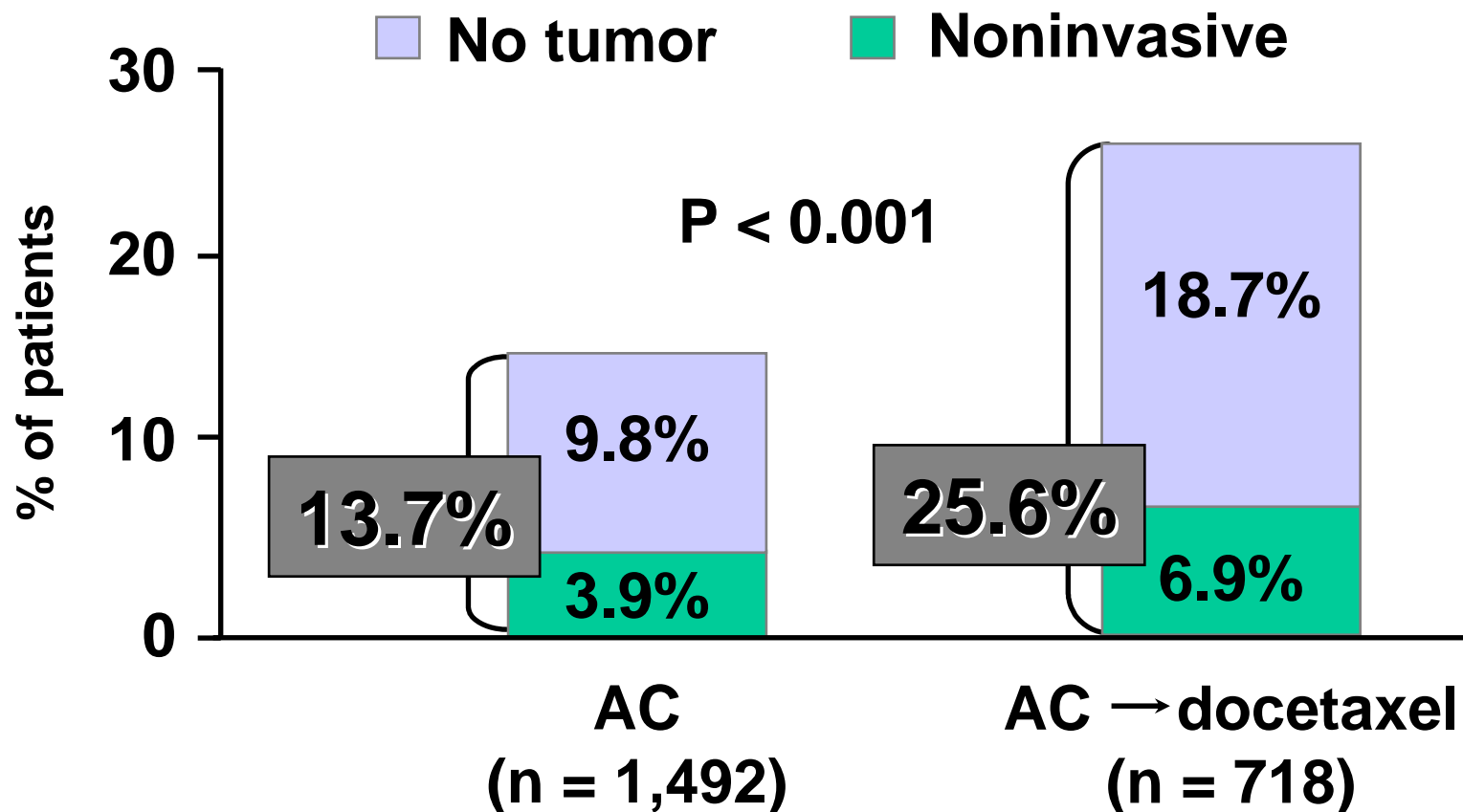
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NSABP B-27 Trial (cont.) Clinical Response



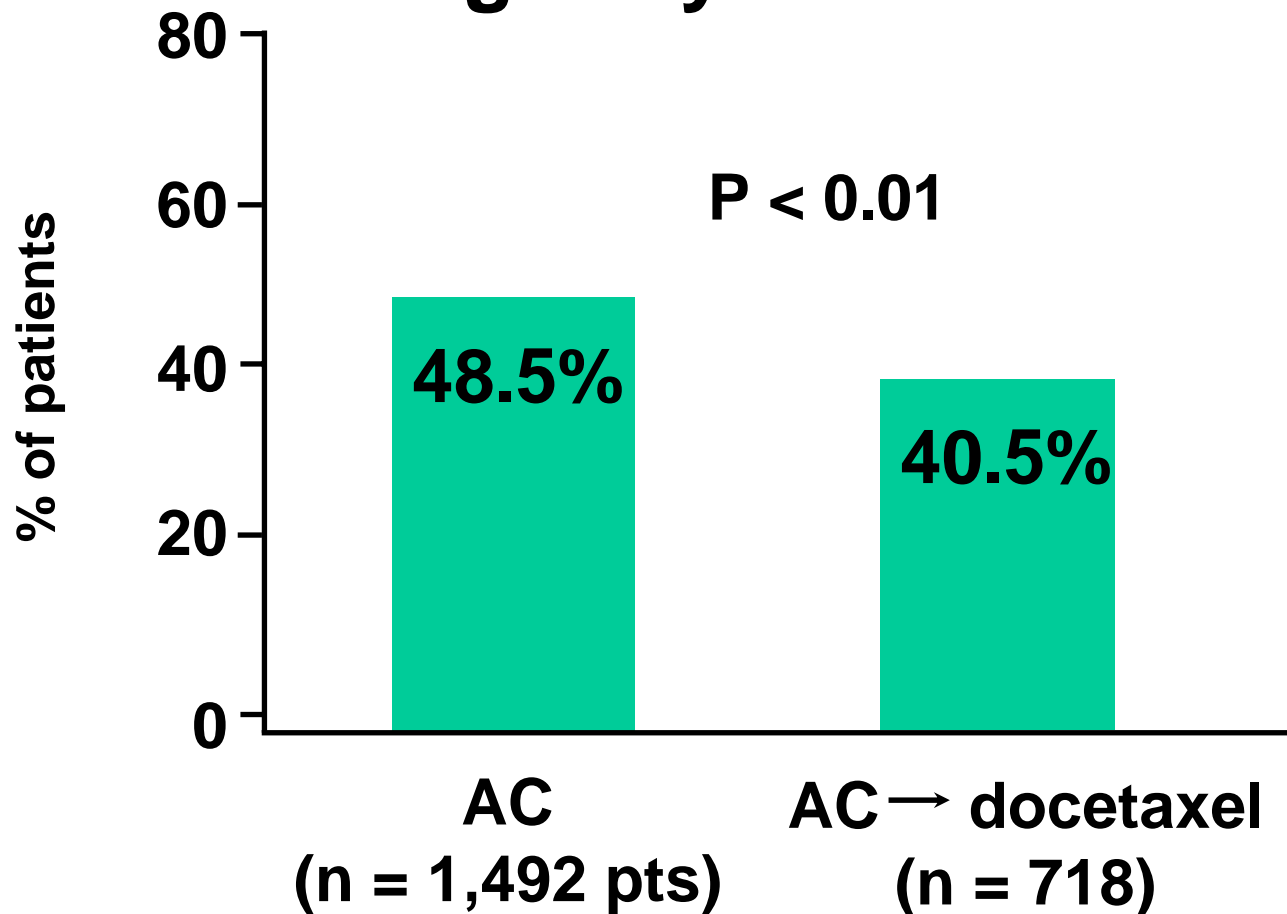
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NSABP B-27 Trial (cont.) Pathologic Complete Response

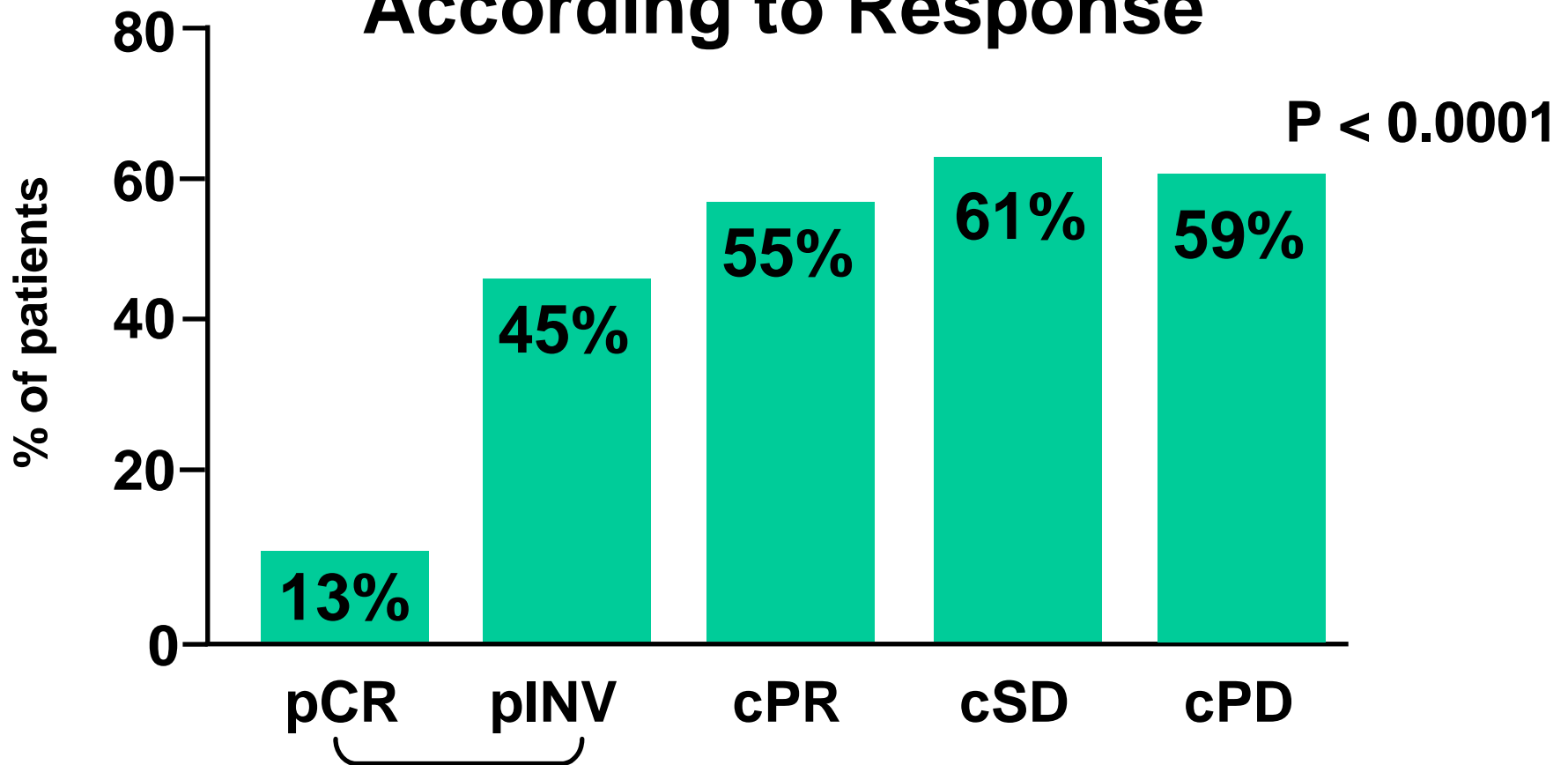


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NSABP B-27 Trial (cont.) Histologically Positive Nodes

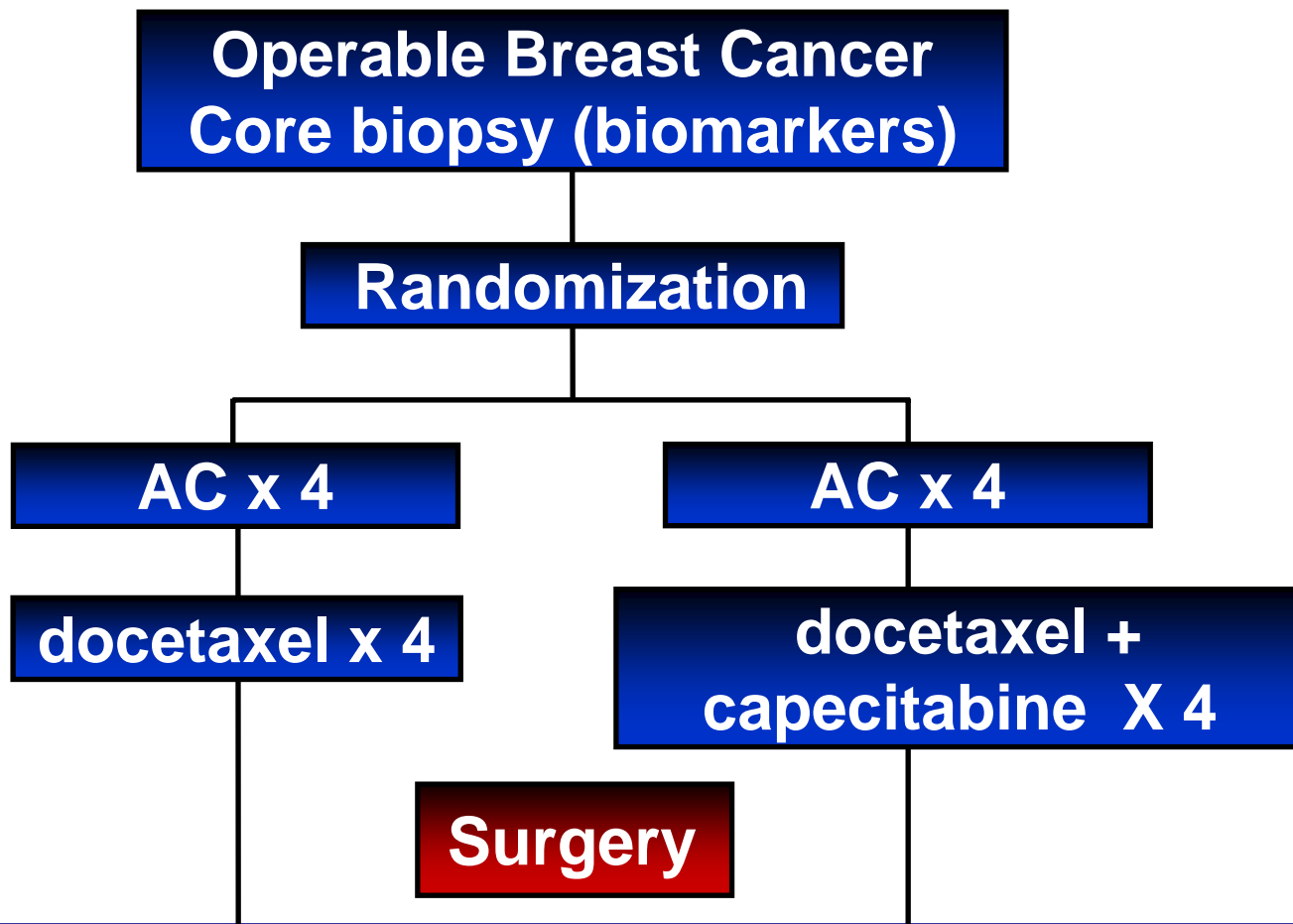


NSABP B-27 Trial (cont.) Histologically Positive Nodes According to Response



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NSABP Neoadjuvant Trial: Concept



Neoadjuvant Docetaxel Trial by Aberdeen Breast Group

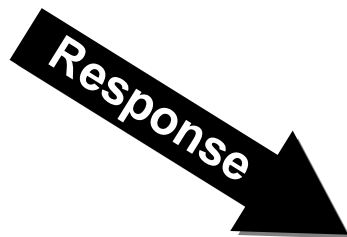
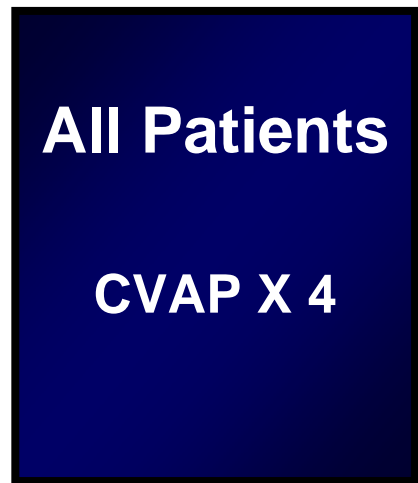
- Randomized trial
- Single-agent docetaxel compared with anthracycline-based polychemotherapy regimen
- 145 patients
- Large (>3cm) or locally advanced (T3, T4, Tx N2) breast cancer
- No prior therapy

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Neoadjuvant Docetaxel Trial (cont.)

First Phase

Second Phase



OR



Final Assessment / Surgery

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Neoadjuvant Docetaxel Trial (cont.) Patient and Tumor Characteristics

	Randomized CVAP	Randomized Docetaxel	Nonrandomized Docetaxel
Mean age (yrs.)	51.71	52.56	52.78
Tumor stage (%)			
T2	42	40	29
T3	42	46	38
T4	17	14	33
Mean tumor diam. (mm)	48.9	45.3	50.8

Neoadjuvant Docetaxel Trial (cont.) Response Rates: First Phase

Objective Clinical Response	% of Pts. (N =145)
Overall	67
Complete	16
Partial	51
Stable disease	32
Progressive disease	1

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Neoadjuvant Docetaxel Trial (cont.) Response Rates: Second Phase (Patients with Response)

Objective Clinical Response	CVP (N = 50)	Docetaxel (N = 47)
Overall	66	94*
Complete	34	62
Partial (additional)	32	32
Partial (maintained)	30	6
Progressive disease	4	0

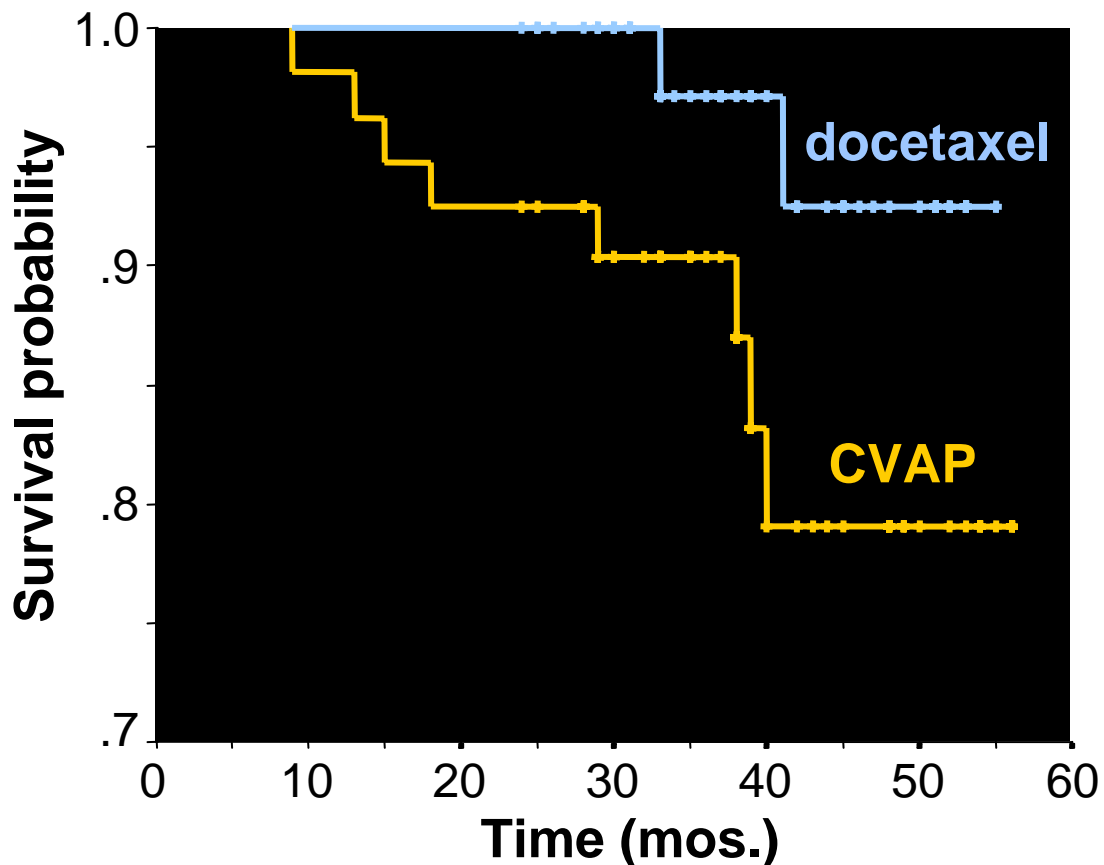
*p = 0.001

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Neoadjuvant Docetaxel Trial (cont.) Response Rates: Second Phase (Patients without Response)

Objective Clinical Response	% of Pts. (N = 48)
Overall	55
Complete	13
Partial	42
Stable disease	35
Progressive disease	10

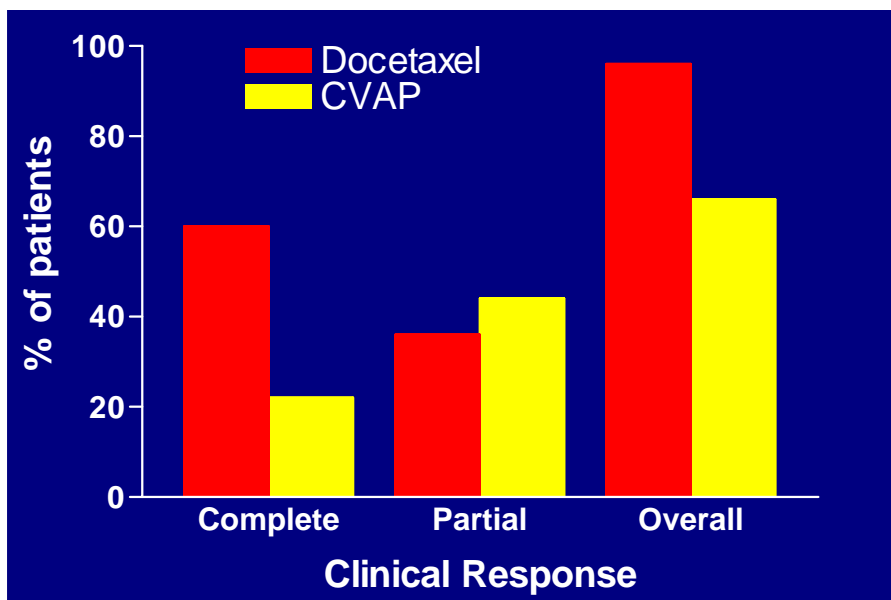
Neoadjuvant Docetaxel Trial (cont.) Survival



- Patients who responded to CVAP
- Randomized to: docetaxel x 4 or CVAP x 4
- Survival increased in docetaxel group

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Neoadjuvant Docetaxel Trial (cont.) Clinical Responses and Type of Surgery

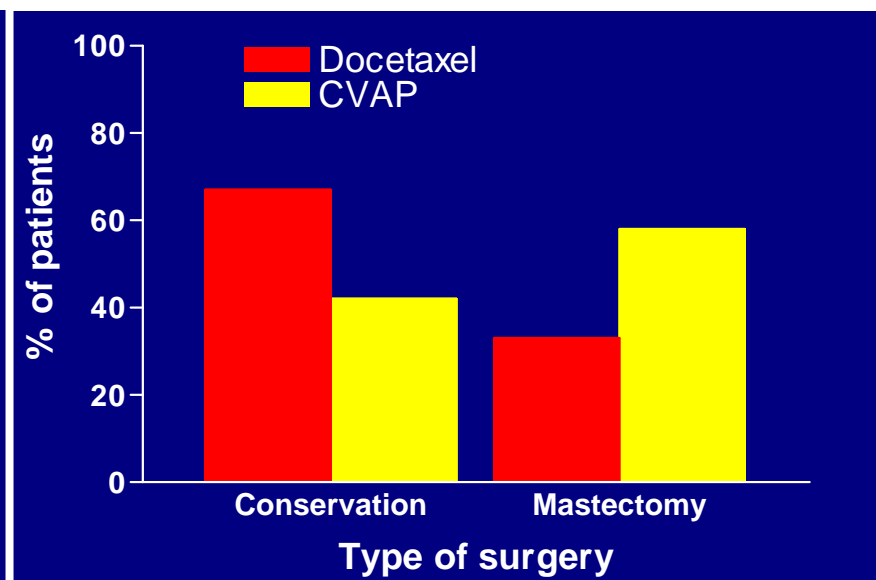


Overall response rate

Docetaxel: 94%

CVAP: 66%

P < 0.001



Breast-conserving surgery

Docetaxel: 67%

CVAP: 48%

P < 0.01

Update on Studies with Trastuzumab

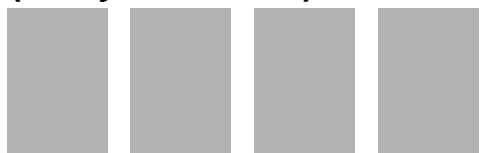
- Survival advantage with chemotherapy and trastuzumab in the metastatic setting
- Trastuzumab in adjuvant setting produced spectacular results with 50% decrease in recurrence
- Alternative approach is to introduce trastuzumab in the neoadjuvant setting, where response to therapy can provide an intermediate endpoint for the impact of trastuzumab on survival in early breast cancer

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Schema of Trials of Neoadjuvant Trastuzumab

Induction chemotherapy
(fluorouracil, epirubicin,
cyclophosphamide)

(every 3 wks. x 4)



Assess
clinical
response
→

Definitive
breast
surgery

Assess
pathologic
response
→

± Tamoxifen
± Radiation

(every wk. x 12)



↑ trastuzumab, 4mg/kg first wk.; ↑ trastuzumab 2mg/kg every wk.; ♥ left ventricular ejection fraction

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Neoadjuvant Trastuzumab (cont.)

Treatment Plan

P = paclitaxel, 225 mg/m², 24-hr IV infusion every 3 wks.

P P P P

F F F F
E E E E
C C C C

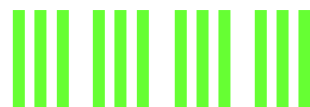
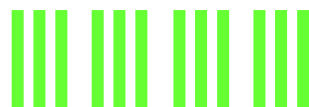
FEC = fluorouracil 500 mg/m² IV, days 1 and 4
epirubicin 75 mg/m² IV, day 1 only
cyclophosphamide 500 mg/m² IV, day 1 only, every 3 wks.

VS

P P P P

F F F F
E E E E
C C C C

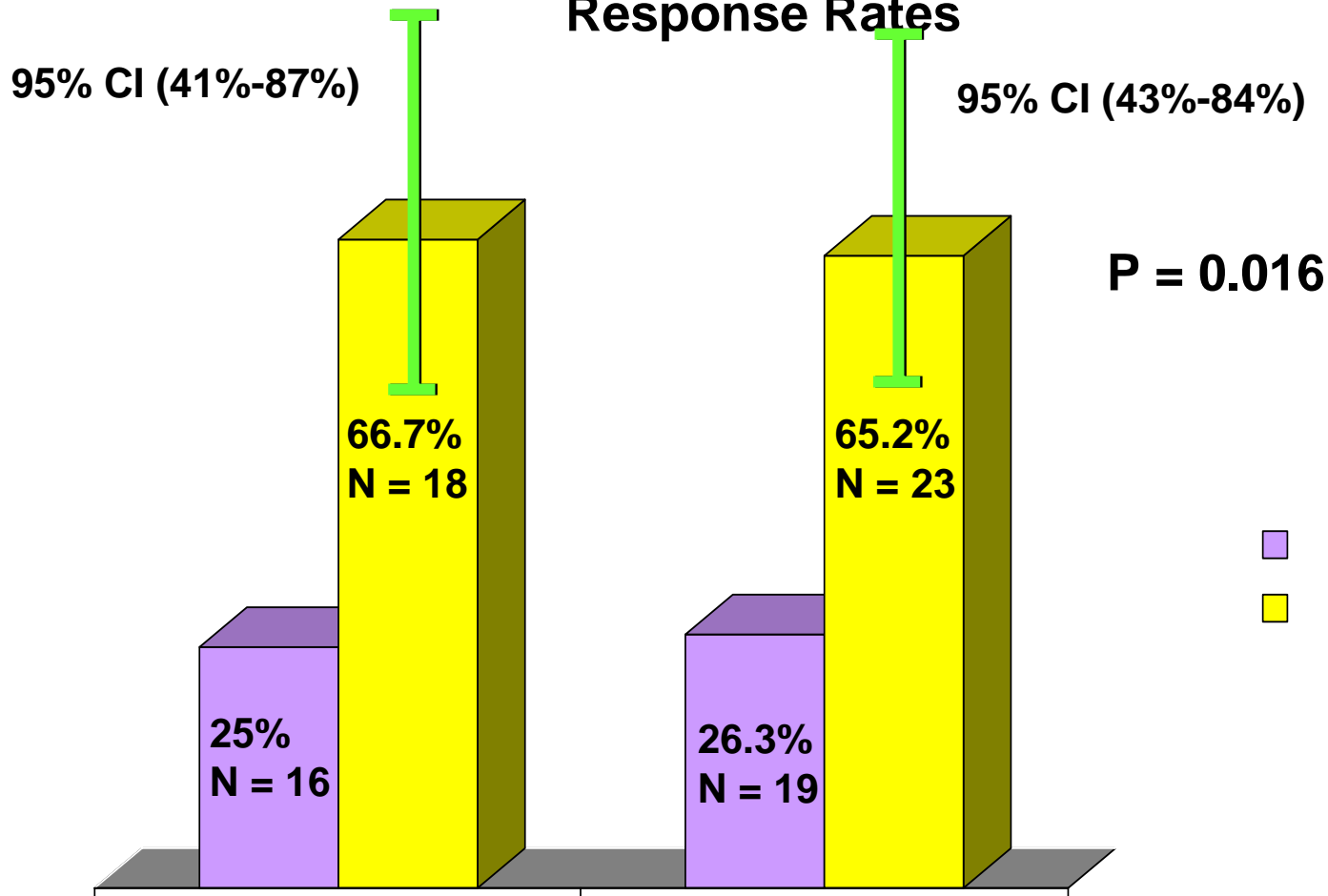
+



Trastuzumab 4 mg/kg IV day 1, then 2 mg/kg IV wkly

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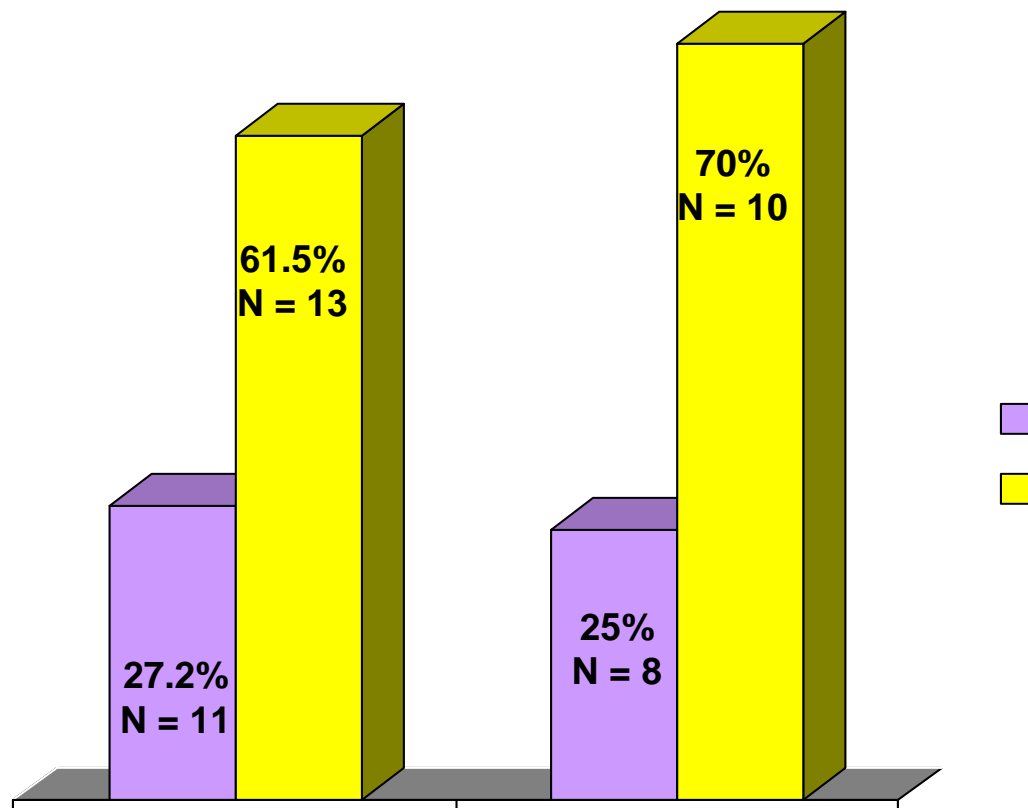
Neoadjuvant Trastuzumab (cont.): Pathologic Complete Response Rates



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Neoadjuvant Trastuzumab (cont.)

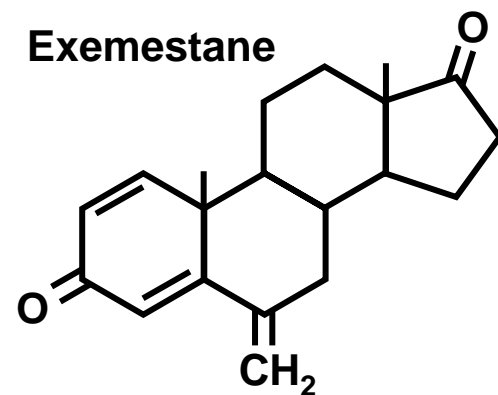
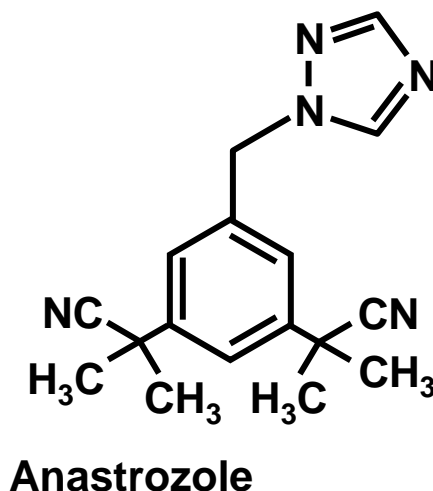
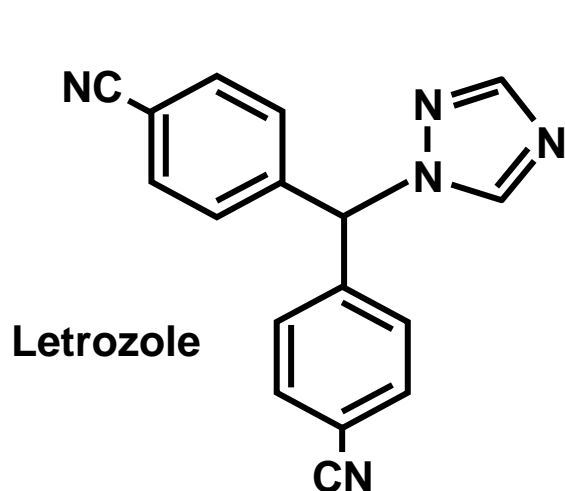
Pathologic Complete Response by Hormone Receptor Status



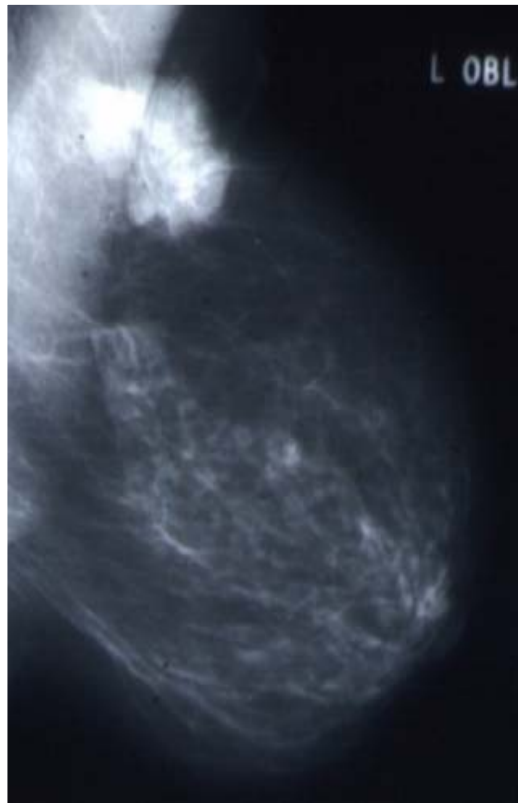
Trials of Neoadjuvant Trastuzumab: Summary of Efficacy

- Preoperative clinical responses observed
 - Overall response rate, 70% to 90%
 - Clinical complete response, 15% to 30%
 - Pathologic complete response, approximately 18%
- Responses higher for patients with 3+ expression of HER2

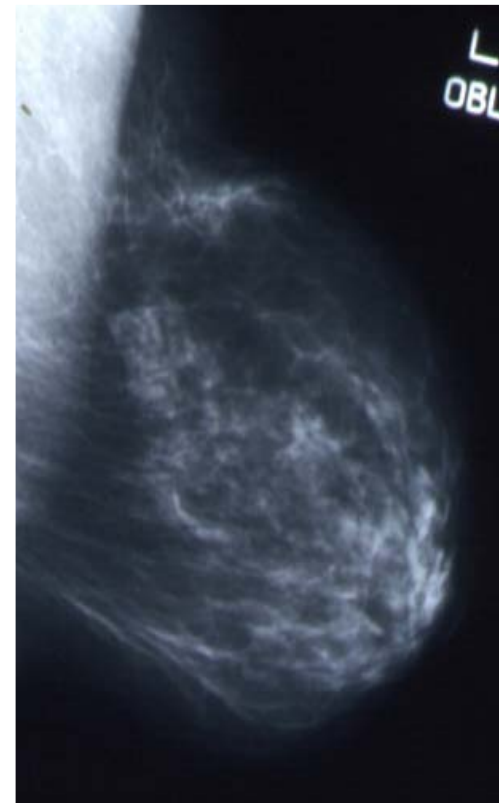
Neoadjuvant Endocrine Therapy: Third-Generation Aromatase Inhibitors



Efficacy of Neoadjuvant Endocrine Therapy



Before treatment

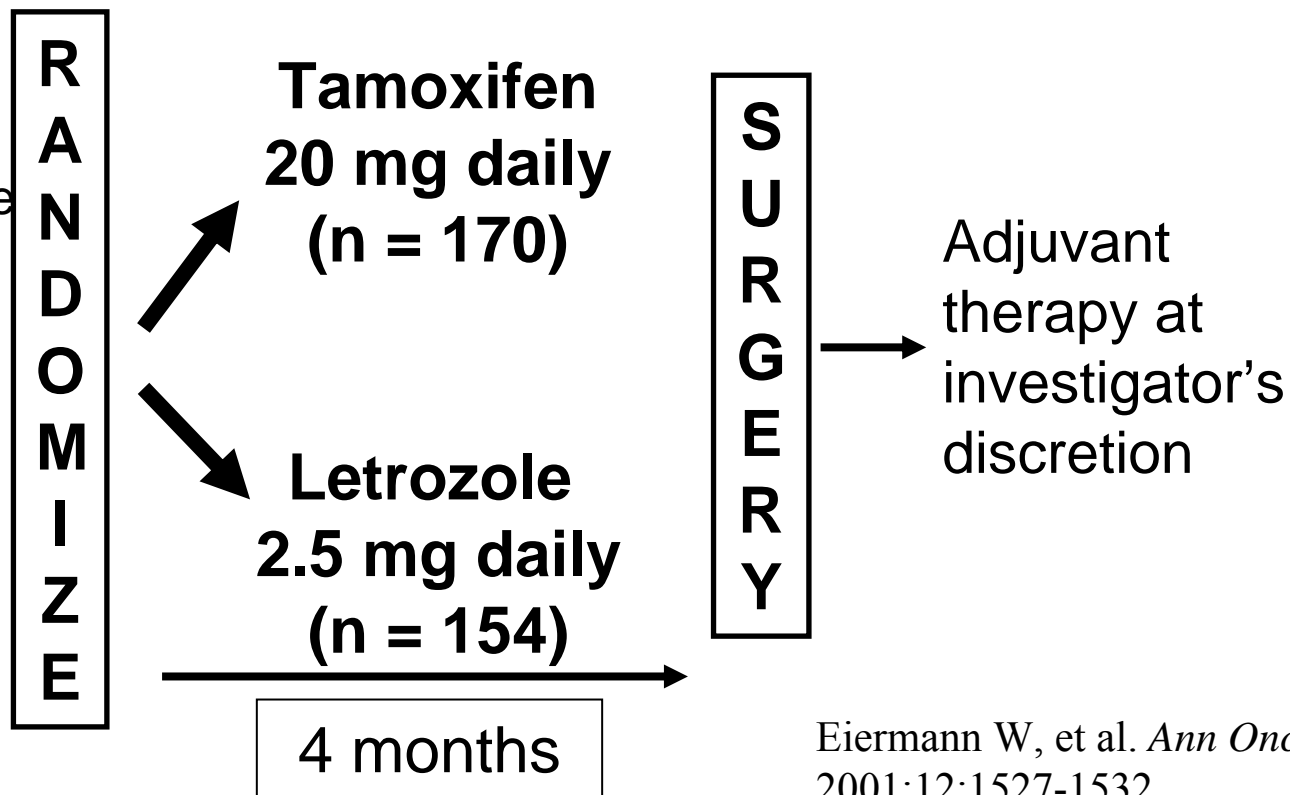


After treatment with letrozole
for three months

Neoadjuvant Tamoxifen Compared with Letrozole

- 55 centers in 16 countries

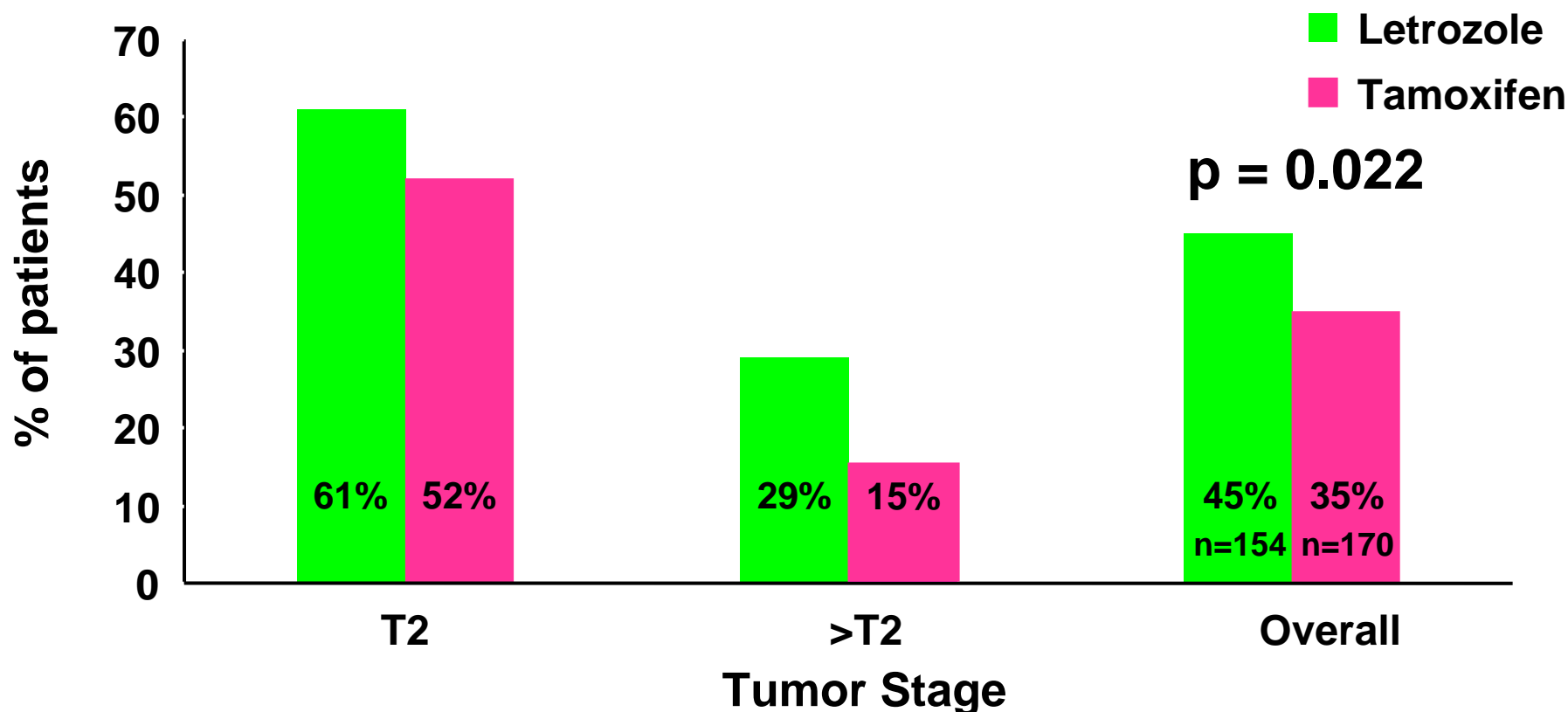
337 postmenopausal women with ER-positive and/or PR-positive disease, not eligible for breast-conserving surgery



Eiermann W, et al. *Ann Oncol.* 2001;12:1527-1532.

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Neoadjuvant Tamoxifen Compared with Letrozole: Breast-Conserving Surgery



Eiermann W, et al. *Ann Oncol.* 2001;12:1527-1532; Newman LA, et al. *Ann Surg Oncol.* 2002;9:228-234.

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Preoperative Endocrine Therapy: Tamoxifen Compared with Aromatase Inhibitors

Study	P024		IMPACT			Semiglazov		PROACT	
	LET	TAM	ANA	TAM	ANA+ TAM	EXE	TAM	ANA	TAM
Duration	16 wks.		12 wks.			16 wks.		12 wks.	
No. of pts.	154	170	113	108	109	36	37	163	151
Response rate (%)	55	36	37	36	39	89	57	50	40
BCS (%)	45	35	46	22	26	39	11	47	38

Radiation Therapy after Mastectomy

According to Consensus Statement developed by American Society for Therapeutic Radiology and Oncology (ASTRO)

- Radiation therapy should be part of the treatment for stage III breast cancers and for disease that involves four or more lymph nodes
- At a minimum, the chest wall and the supraclavicular fossa should be treated with doses of at least 50 Gy

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