

# PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

## After Preoperative Therapy: *“What now?”*

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# Purposes of Preoperative Therapy

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- Deliver effective systemic therapy
- Downstage tumor for surgery
- Assess dynamic response to therapy
  - Populations / research
    - Define efficacy of treatment regimen using surrogates for long-term outcomes
  - Individuals / clinical practice
    - Inform prognosis
    - Tailor treatment program based on response

# Outline: After Preoperative Therapy

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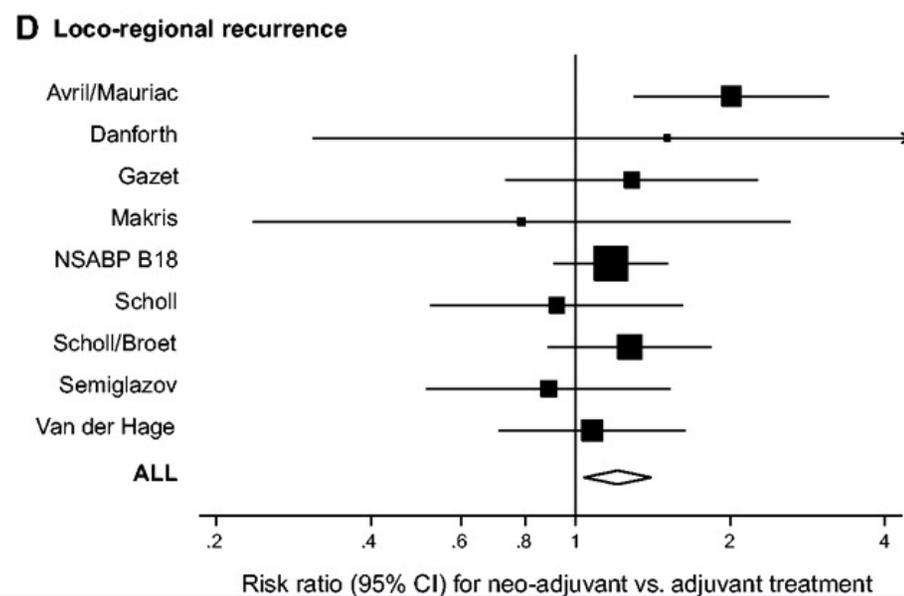
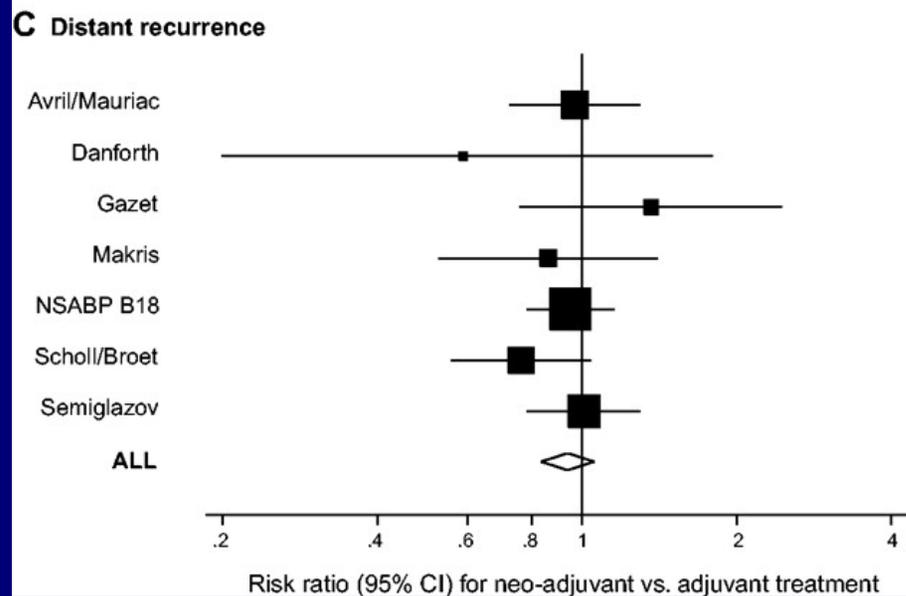
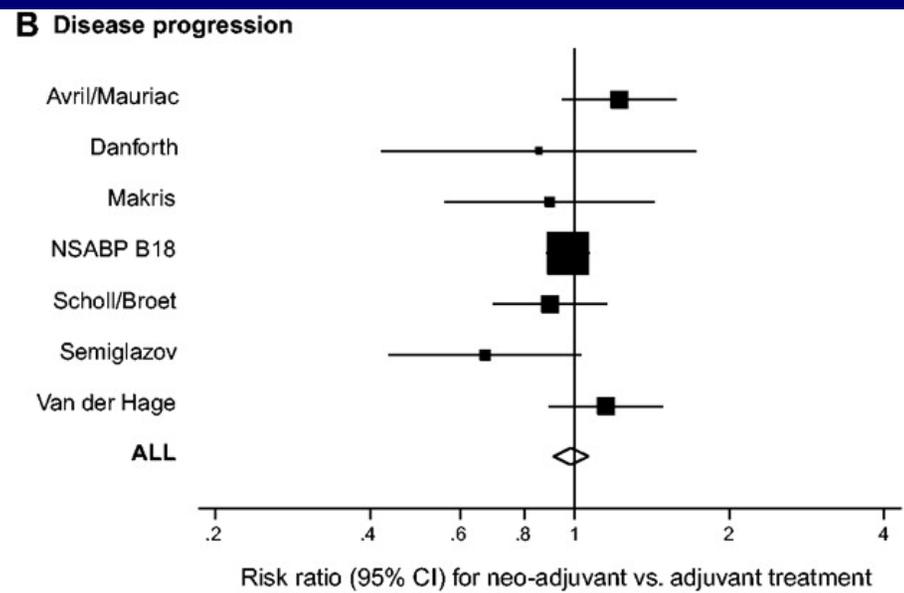
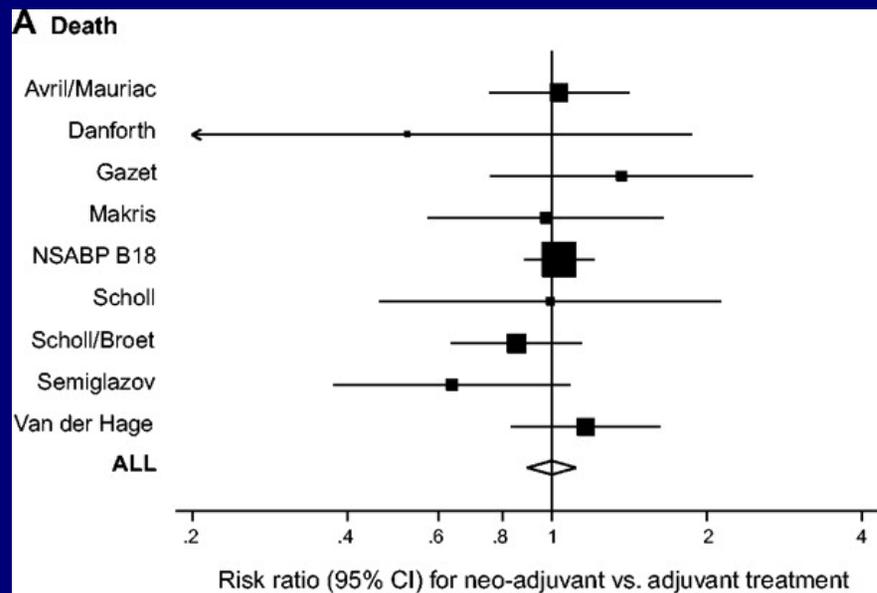
1. Surveillance
2. Systemic Therapy

# Local-regional Recurrence after Preoperative Therapy

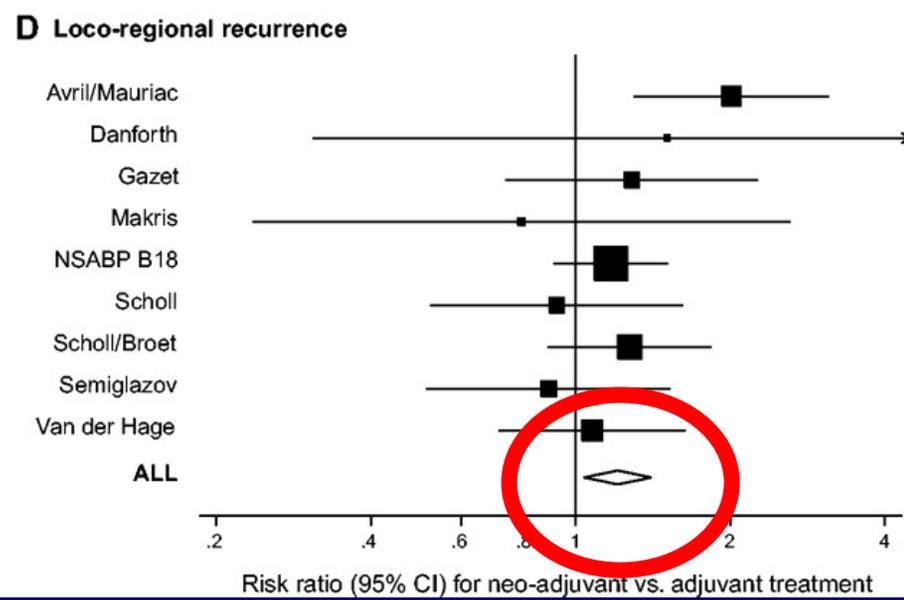
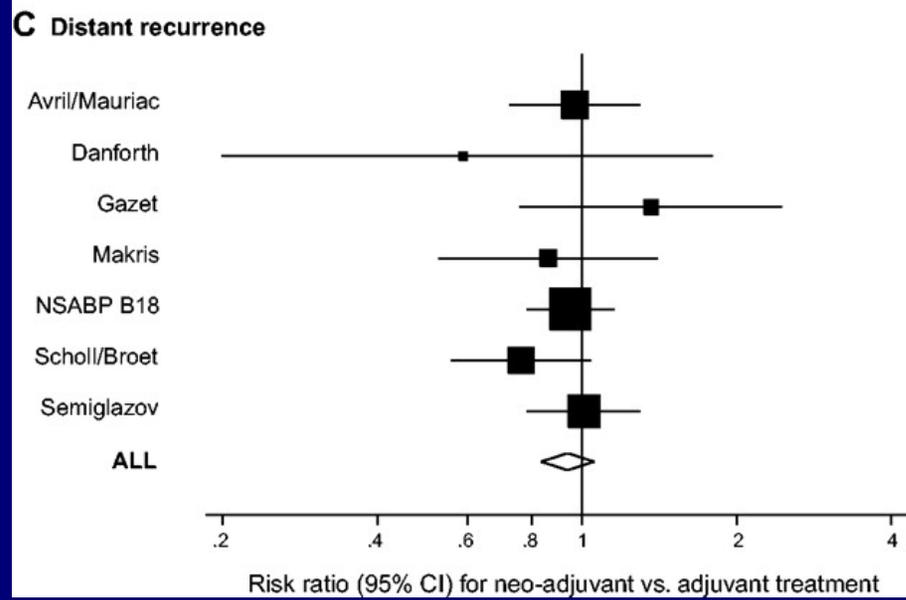
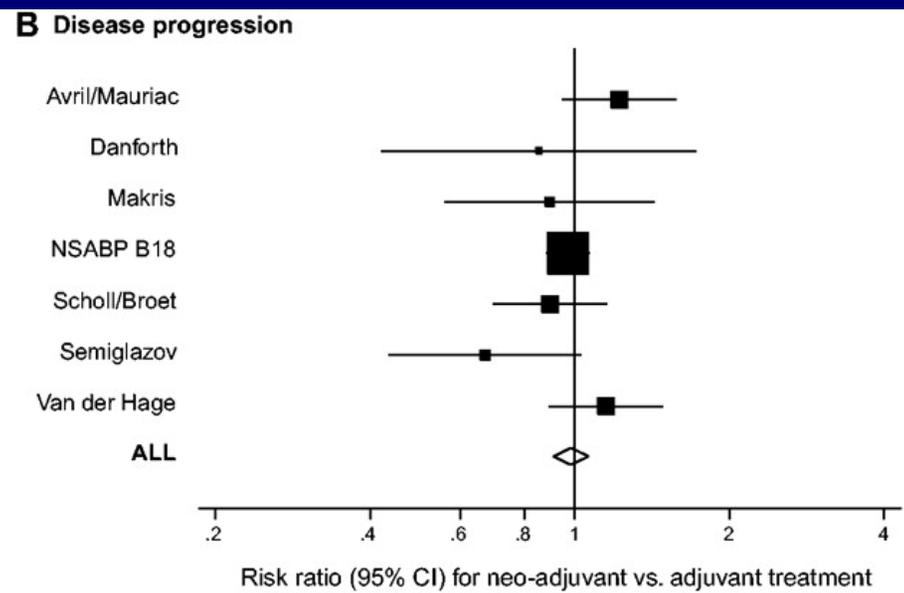
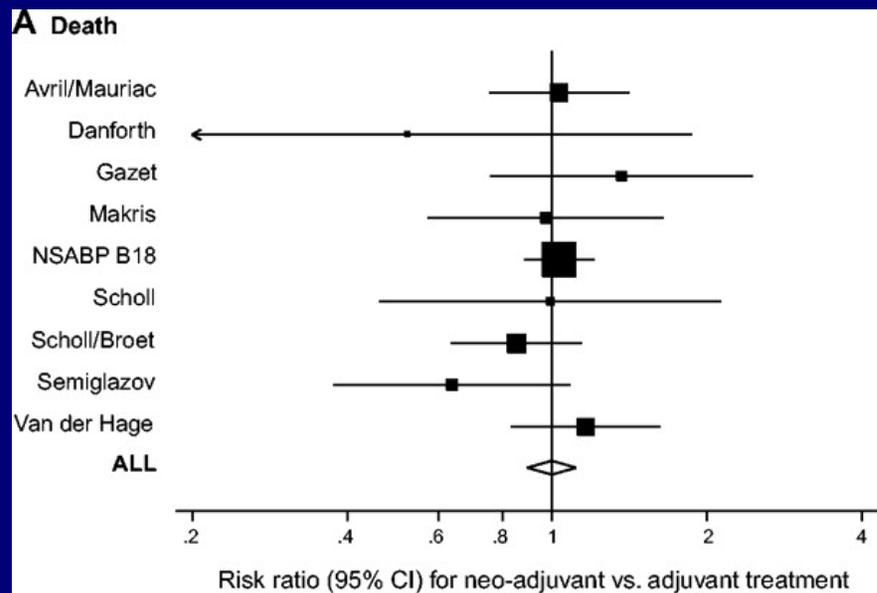
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- The goal of preoperative therapy is surgical downstaging
- More patients are likely to have BCS after preoperative therapy
- Patients with BCS after preoperative therapy *may* be at higher risk for local-regional recurrence
- Local-regional recurrence constitutes a substantial percentage of breast cancer events in neoadjuvant patients, owing perhaps to higher stage at diagnosis

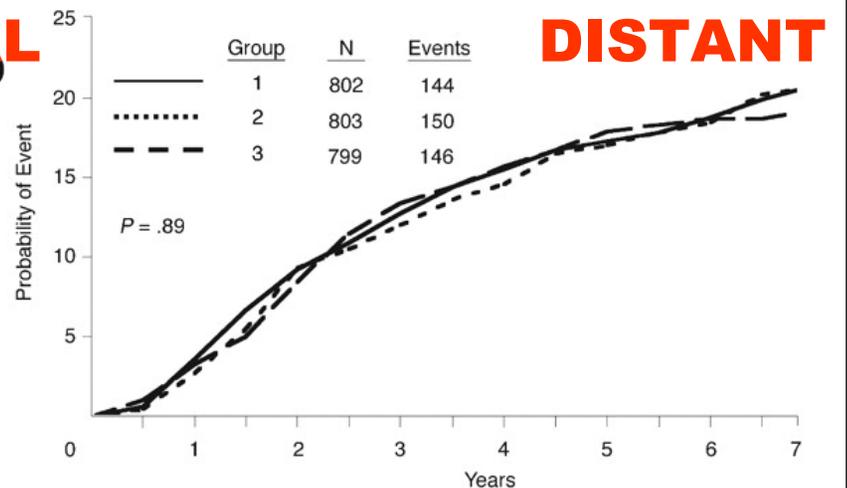
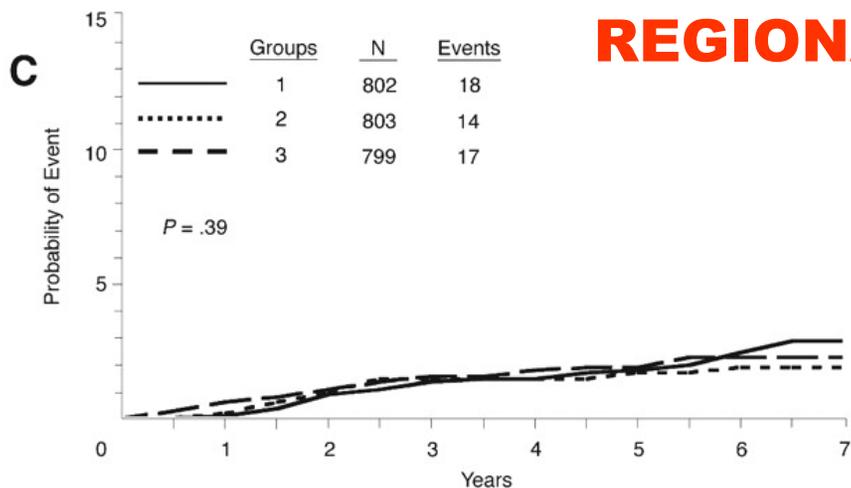
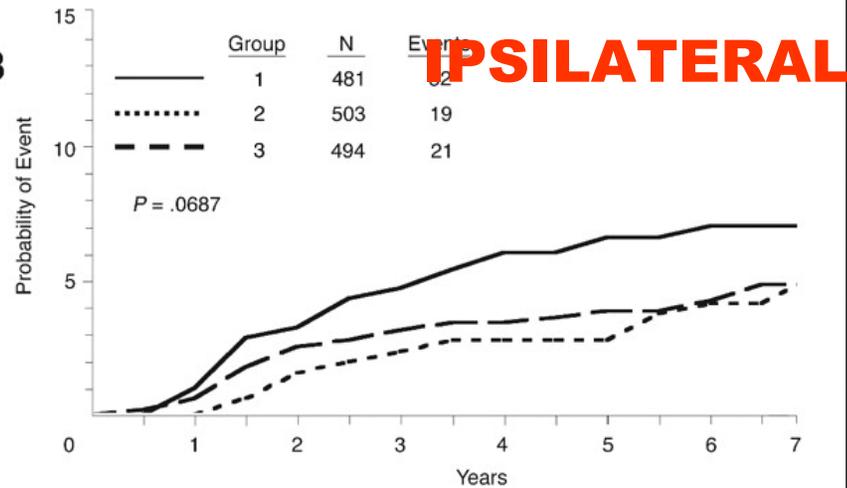
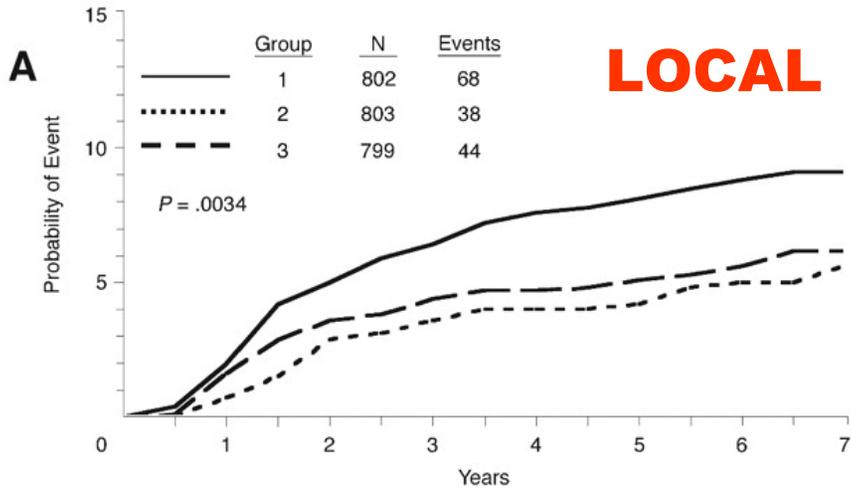
# Neoadjuvant therapy compared with adjuvant therapy for breast cancer



# Neoadjuvant therapy compared with adjuvant therapy for breast cancer



# Recurrences in NSABP B-27



# Local-regional surveillance

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- No unique guidelines exist for local-regional surveillance after preoperative therapy
- Because of risk of local-regional events, clinicians should offer standard surveillance with a low threshold to further evaluate changes

# Systemic Therapy and Surveillance After Preoperative Therapy

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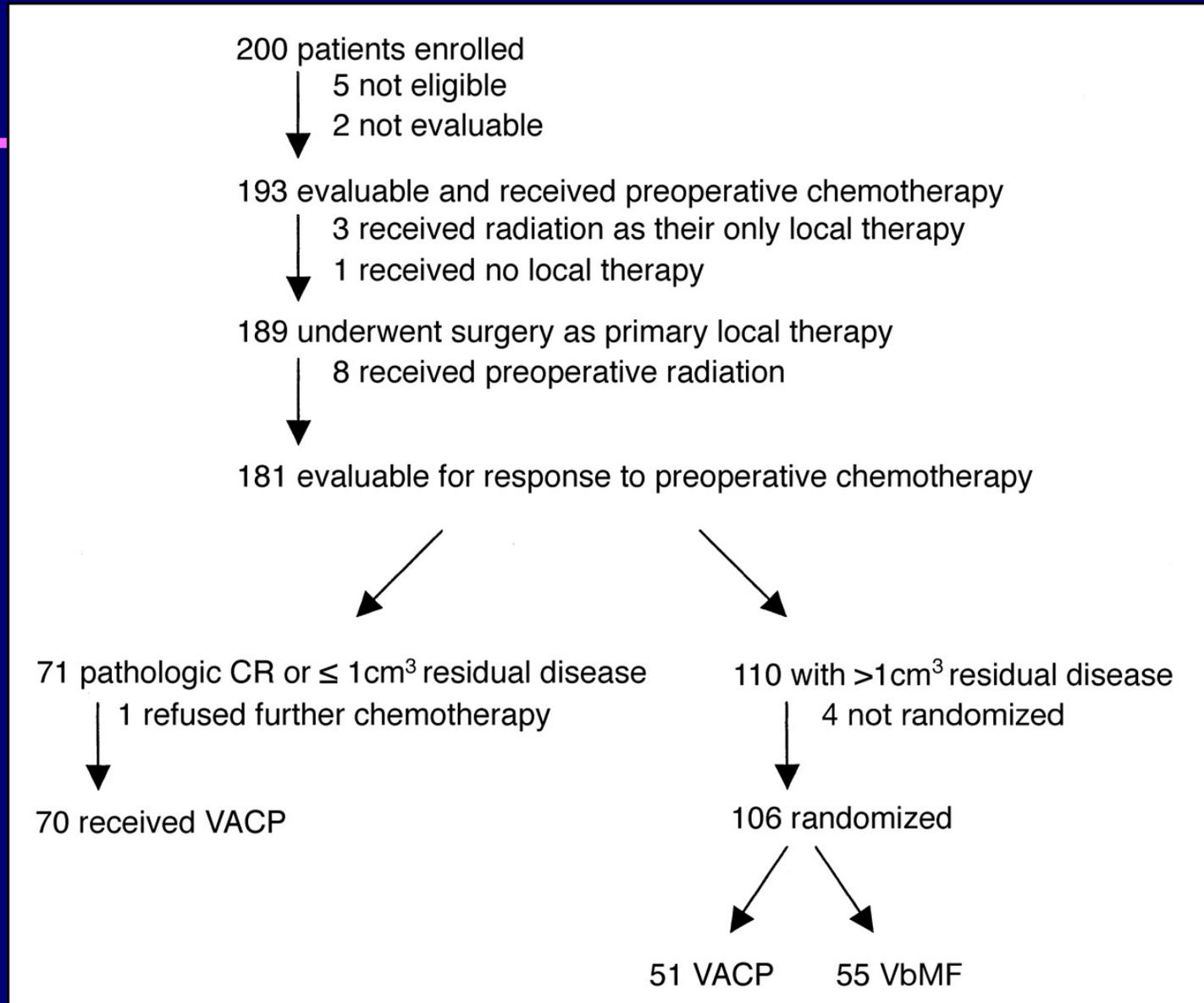
- All patients should receive standard biological adjuvant therapy
  - anti-estrogen therapy for ER+ tumors
  - anti-HER2 therapy (i.e. trastuzumab) for HER2+ tumors
- Surveillance for recurrence according to standard recommendations (e.g. ASCO)
- Threshold for evaluation of symptoms affected by residual risk, which may be informed by results of preoperative therapy

# Systemic Therapy After Preoperative Therapy

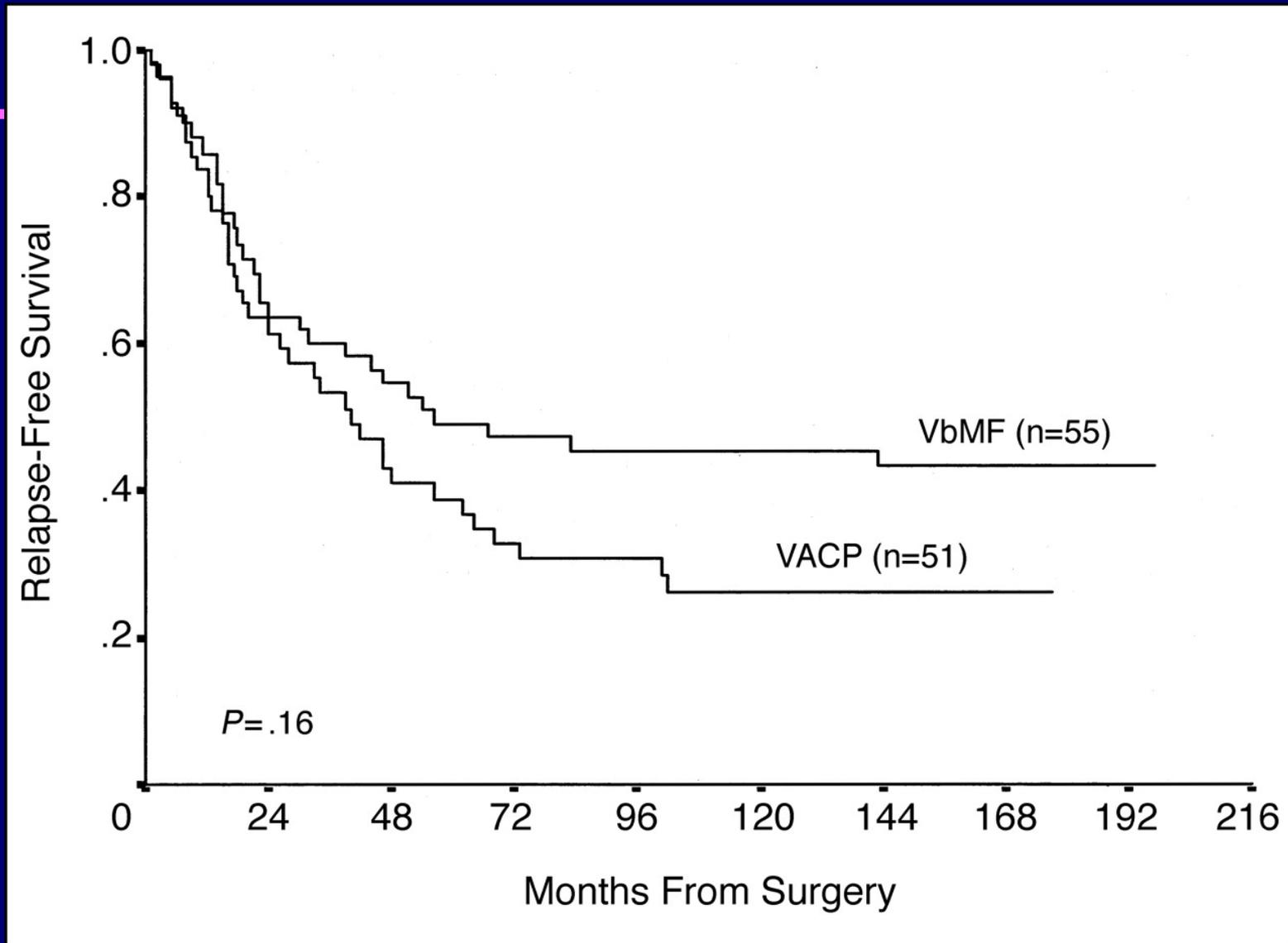
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- Is there a role for additional chemotherapy in patients with residual cancer after neoadjuvant chemotherapy?

# MDACC – Randomized Trial of Adjuvant Chemotherapy after Preoperative Chemotherapy



# Relapse-free survival by randomized treatment arm (dated from surgery)

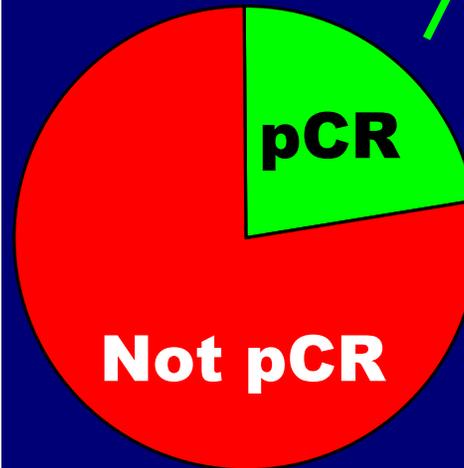
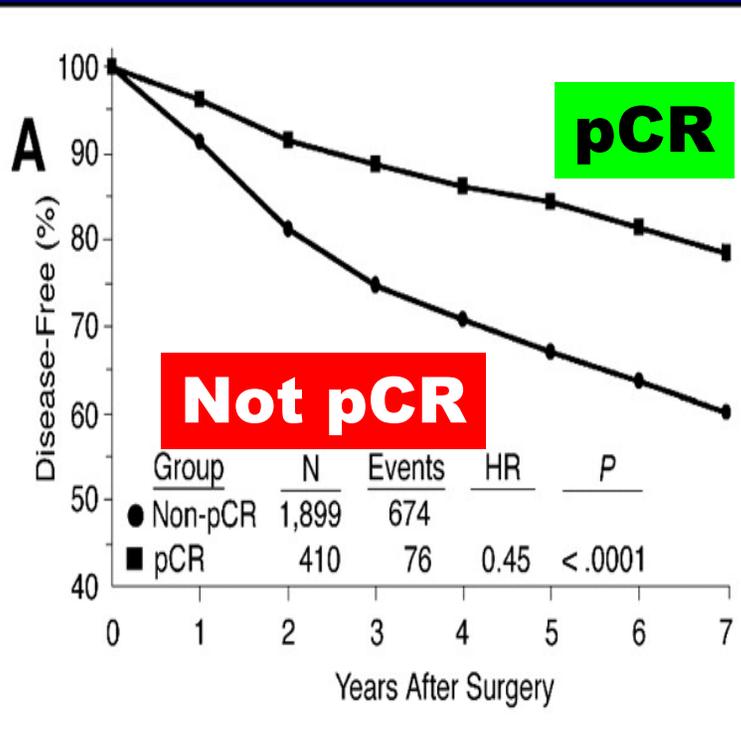


# Systemic Therapy After Preoperative Therapy

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- In 2007, role for further chemotherapy is entirely unclear, and is a common clinical dilemma
  - Vast majority of patients will NOT have pCR, and are at greater risk of recurrence
  - Such patients have tumors that carry, by definition, some clinical resistance to chemotherapy
  - Many – if not all – patients will have had anthracycline-, alkylator- and taxane-based therapy (i.e. no standard “non-cross-resistant” options)
  - There are no data from the modern era to guide treatment recommendations for patients who have completed “standard” adjuvant chemotherapy regimen
  - In the absence of such data, additional chemotherapy should not routinely be administered

# NSABP B-27 Disease-free Survival



**Would more Rx be better?**

*Yes: tumor really sensitive to chemo*  
*No: pt doing well already*

**Would more Rx be better?**

*Yes: high risk warrants therapy*  
*No: tumor resistant already*

# The Post-Preoperative Patient: a high priority population for clinical research

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- Substantial heterogeneity in clinical practice
- No standard consensus on best treatment approach following standard chemotherapy
- Higher risk of recurrence
- Relative resistance to established chemotherapy options
- Begins to deliver on the promise / premise of neoadjuvant therapy that treatment can be tailored based on dynamic response to therapy

# The Post-Preoperative Patient: a high priority population for clinical research

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## Platform for Research Concepts

- Marker analyses for recurrence risk
  - Systemic
  - Local-regional
- Serial monitoring for early detection of recurrence
  - Systemic
  - In-breast
- Therapeutic intervention trials
  - “more therapy”
  - novel therapies

# Surgery for Primary breast cancer within last 3 years

Stage ypT2-4 and / or ypN1-3, and M0

prior preoperative taxane-anthracycline containing chemotherapy

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**Stratification:**  
Receptor status  
Time since surgery  
Age  
Center

**R**



**Observation**

**Zoledronate 4 mg**

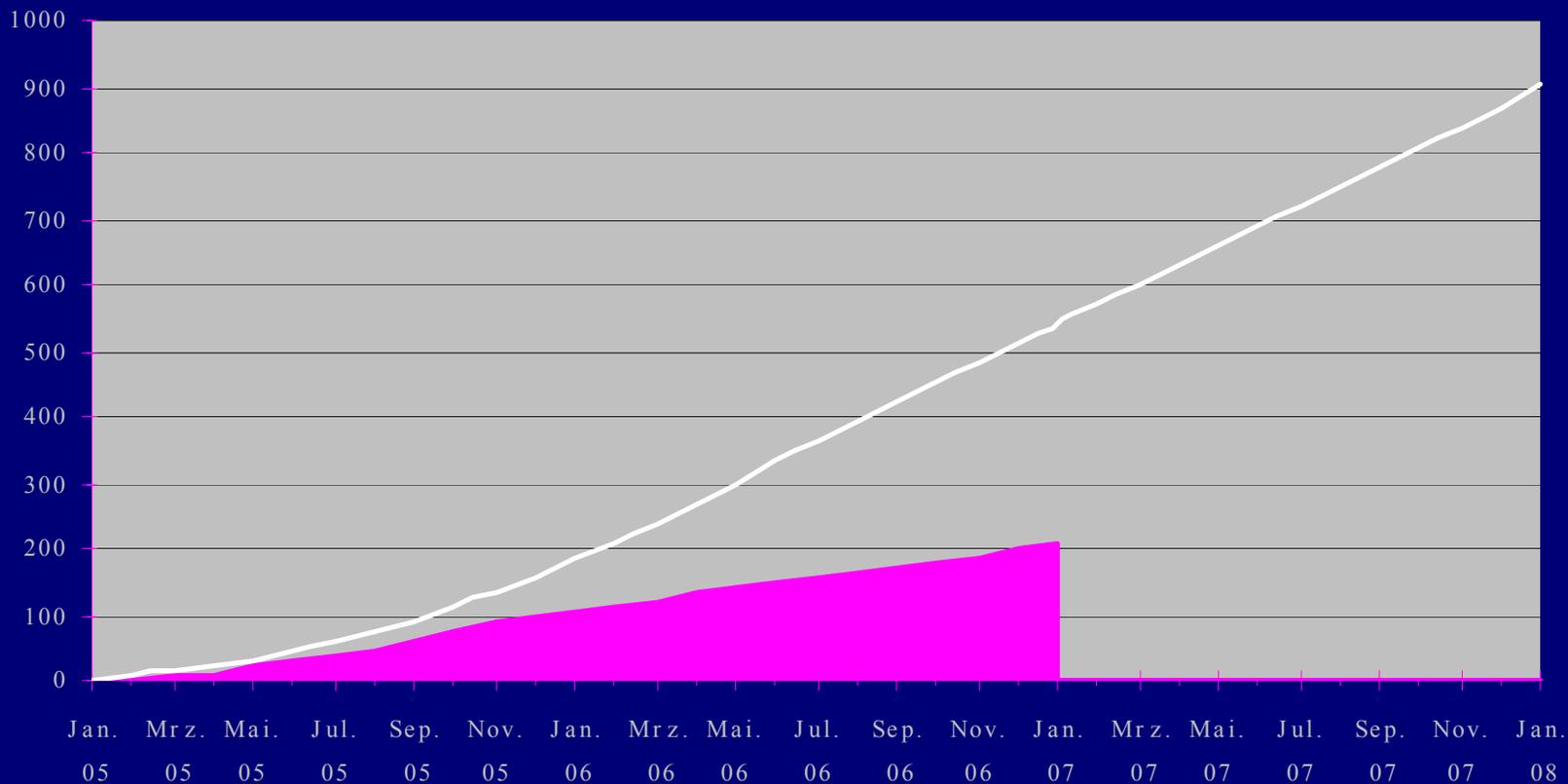
Every 4 weeks for the first 6 doses (year 0 to 0.5)  
Every 3 months for 8 doses (year 0.5 – 2.5)  
Every 6 months for 5 doses (year 2.5 – 5)

**Prior and/or simultaneous standard endocrine/antiHer2 treatment**

**Prior and/or simultaneous radiotherapy**

# NaTaN - Recruitment at 01.01.2007

N = 206



# DFCI – IU – UCSF - UNC

## Feasibility Study of Novel Therapies After Preoperative Chemotherapy

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- Rationale: novel therapies needed for patient population with residual invasive cancer after preoperative chemotherapy
- Plan: sequential cohorts of 40 patients
- Endpoints: feasibility and safety of therapy
- Correlative studies: markers of angiogenesis activity, predictors of recurrence

# Pilot Feasibility Study of Novel Therapies After Preoperative Chemotherapy

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## Cohort 1

### Bevacizumab

Bevacizumab 15 mg/kg IV q 21 days x 1 year

## Cohort 2

### Metronomic CM + bevacizumab

Cyclophosphamide 50 mg PO QD

Methotrexate 2.5 mg PO BID days 1,2 each week

Bevacizumab 15 mg/kg IV q 21 days x 1 year

## Cohort 3

### Capecitabine + bevacizumab

Capecitabine 2000 mg/m<sup>2</sup> days 14 of 21 x 6 cycles

Bevacizumab 15 mg/kg IV q 21 days x 1 year

# Proposed Trial for Post Preoperative Therapy

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Standard Neoadjuvant Chemotherapy

Residual Invasive Breast Cancer

anti-VEGF

anti-VEGF  
&  
chemo

chemo

# Summary

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- After preoperative therapy, patients receive standard radiotherapy, biologically-based adjuvant therapy, and surveillance
- Patients who have completed preoperative therapy constitute an important population with *unique* and *unmet* oncological needs
- Substantial opportunities exist to study patients after preoperative therapy to improve their cancer-related outcomes