National Cancer Institute

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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National Institutes of Health

Purposes of Preoperative Therapy

- 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

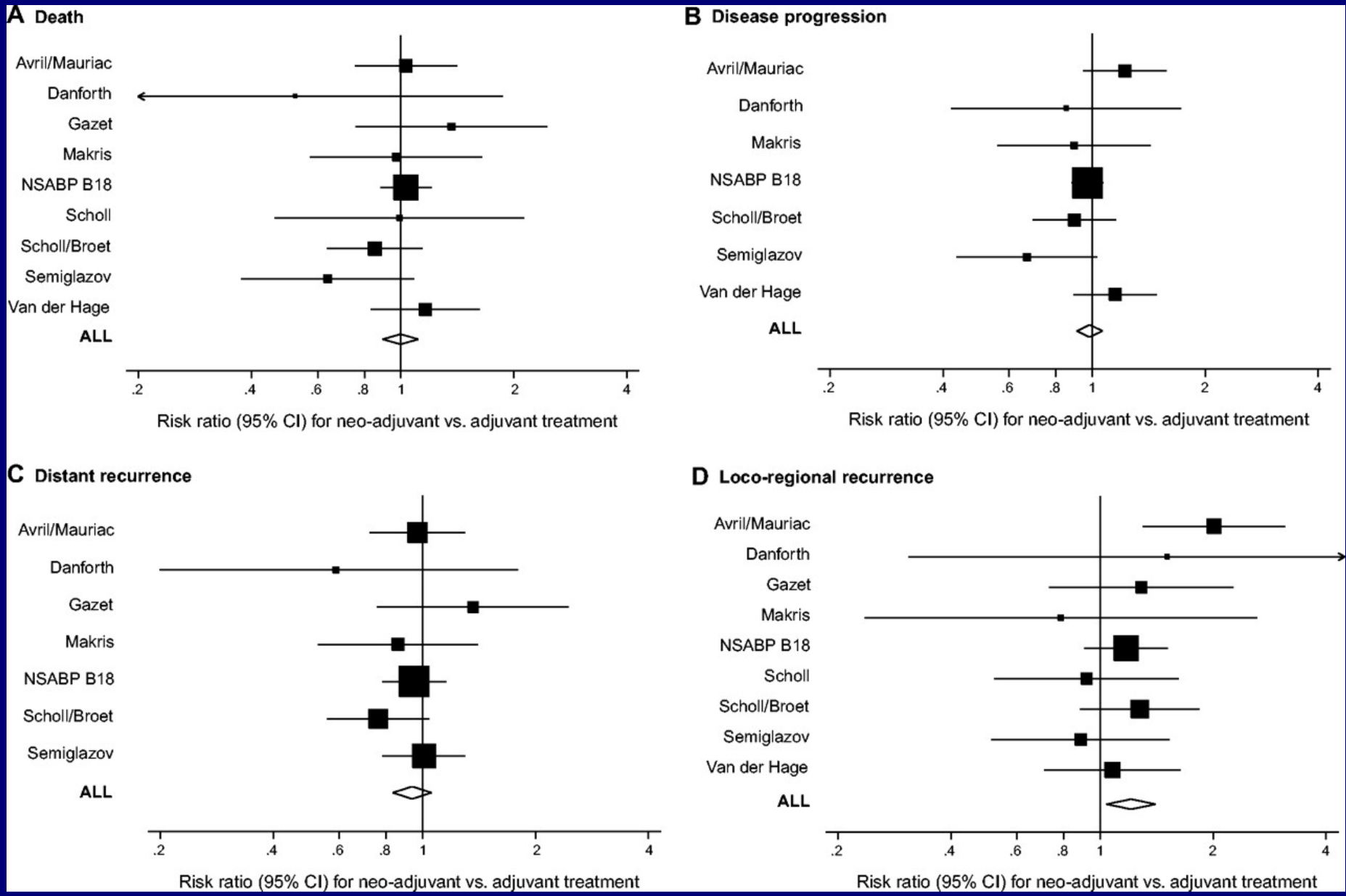
Outline: After Preoperative Therapy

1. Surveillance
2. Systemic Therapy

Local-regional Recurrence after Preoperative Therapy

- 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



Mauri, D. et al. J. Natl. Cancer Inst. 2005 97:188-194; doi:10.1093/jnci/dji021

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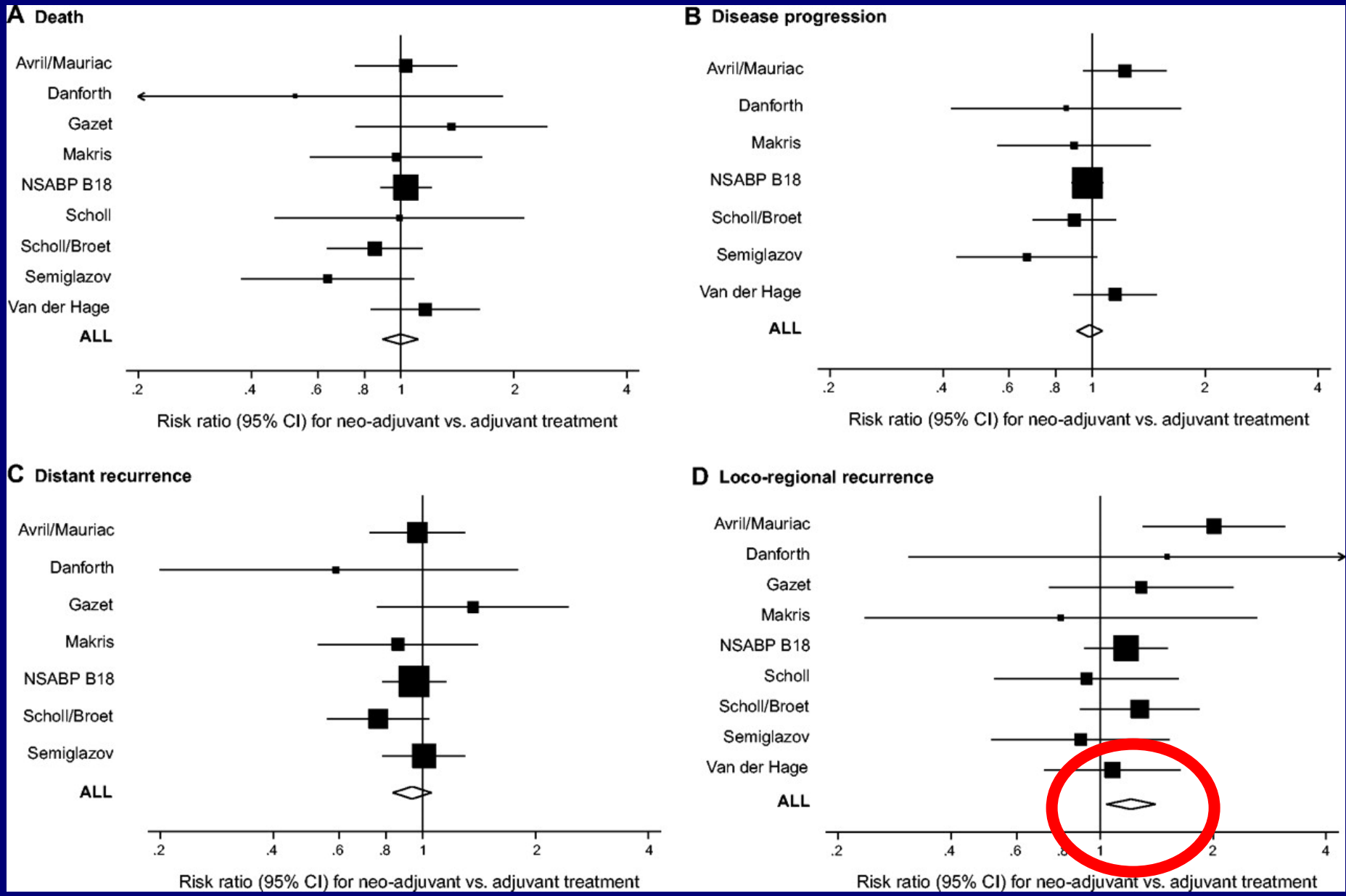

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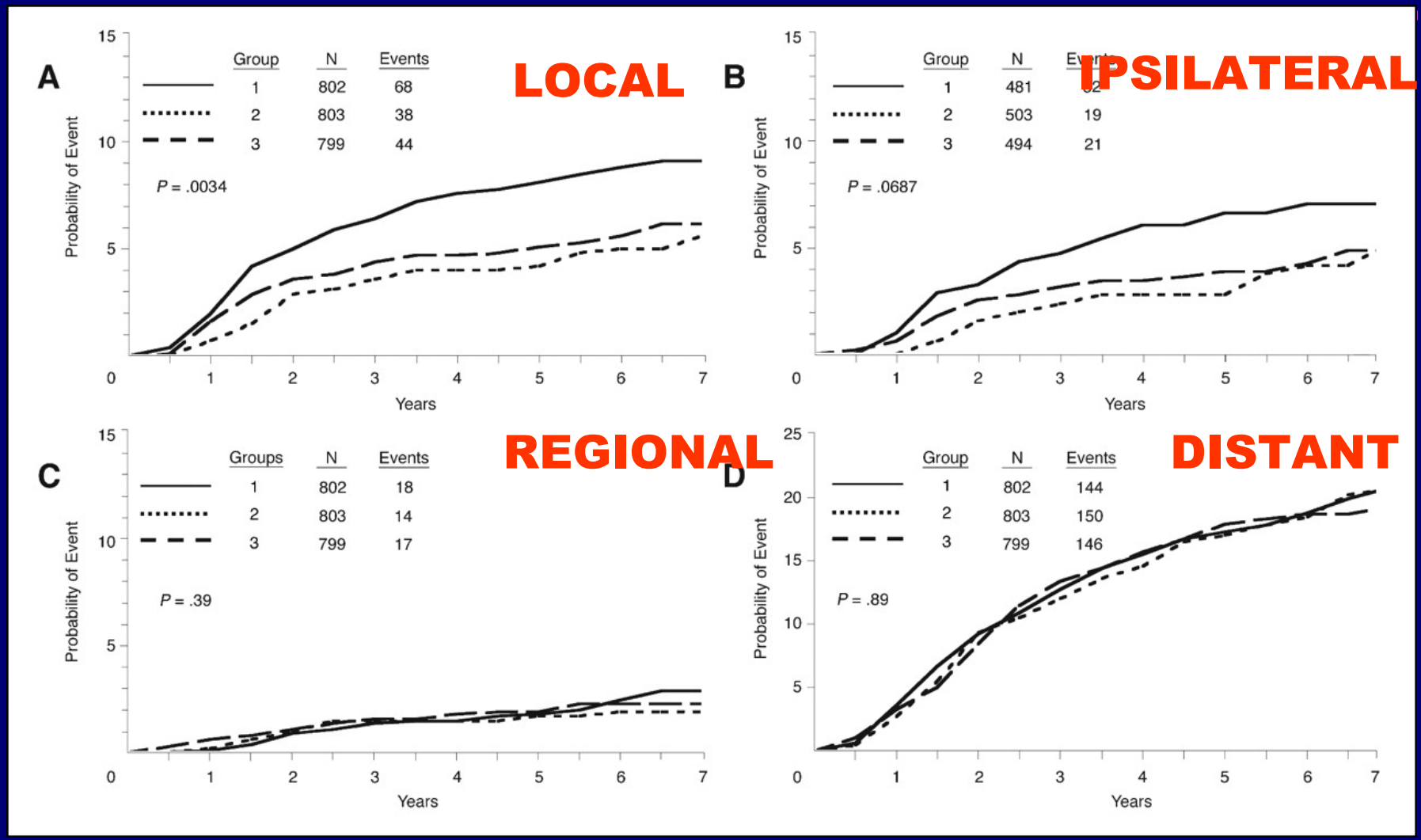
Recurrences in NSABP B-27



Bear, H. D. et al. J Clin Oncol; 24:2019-2027 2006

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Local-regional surveillance

- 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

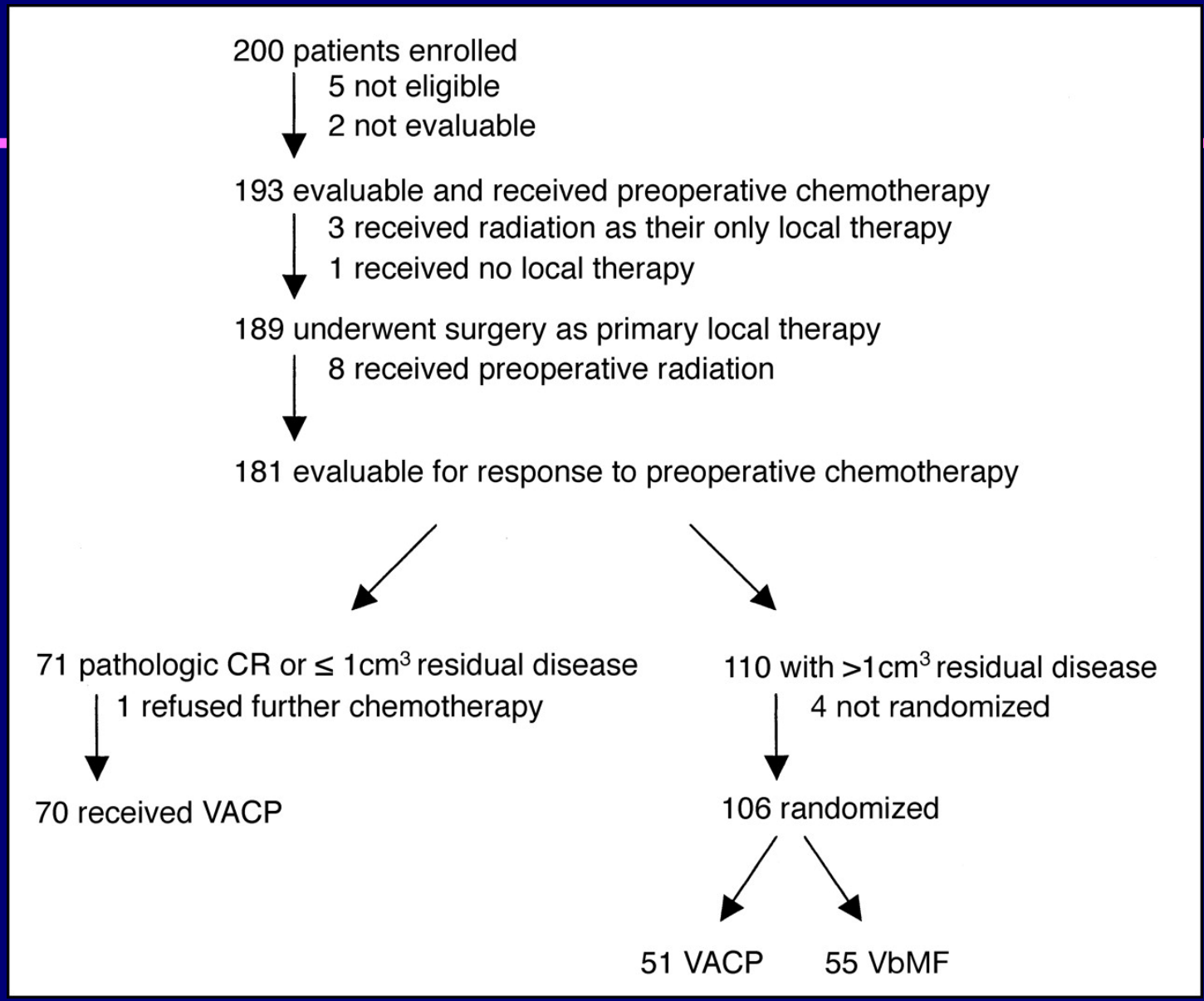
Systemic Therapy and Surveillance After Preoperative Therapy

- 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

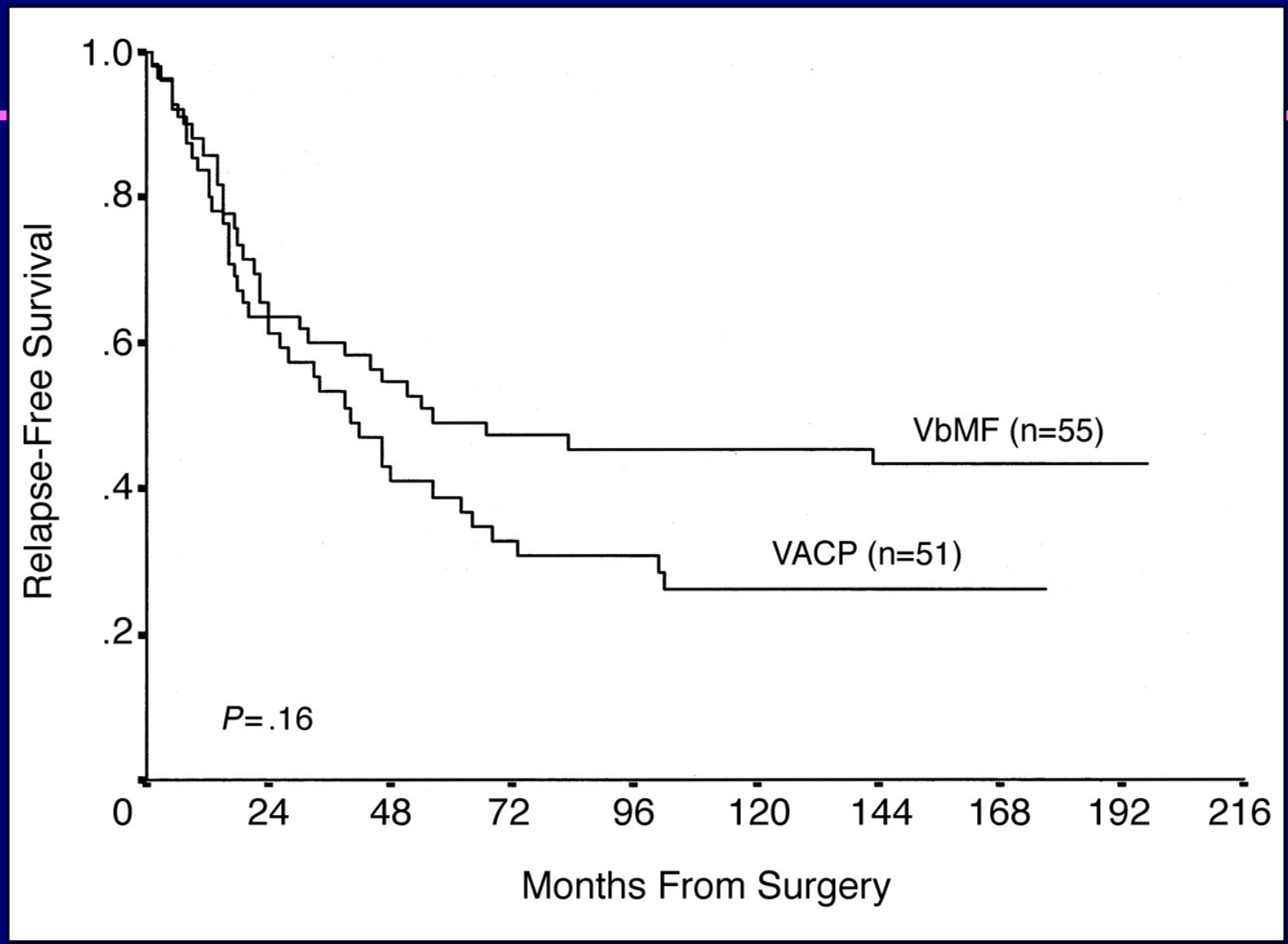
- Is there a role for additional chemotherapy in patients with residual cancer after neoadjuvant chemotherapy?

MDACC – Randomized Trial of Adjuvant Chemotherapy after Preoperative Chemotherapy



Thomas, E. et al. J Clin Oncol; 22:2294-2302 2004

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



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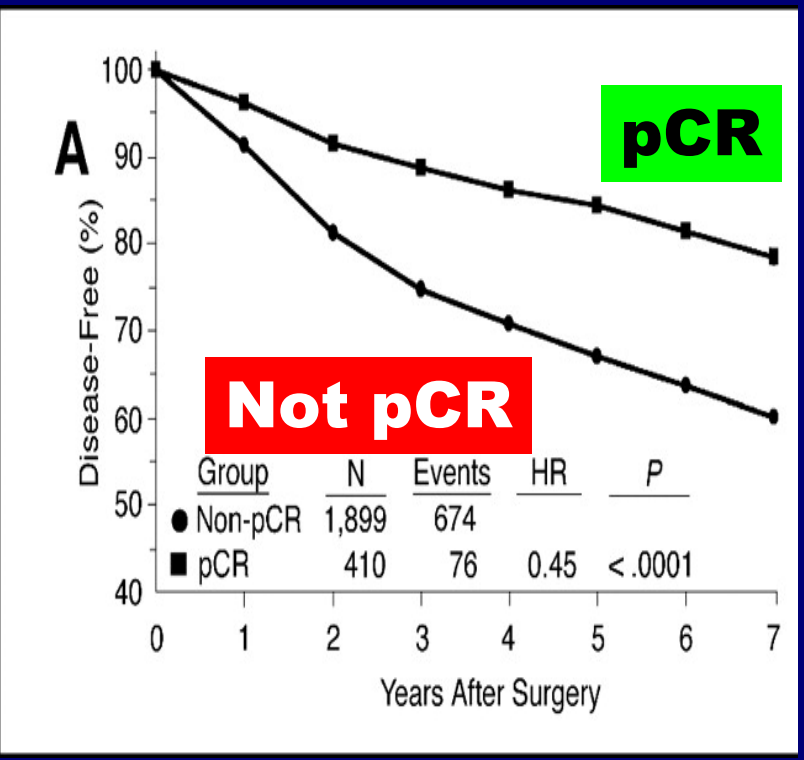
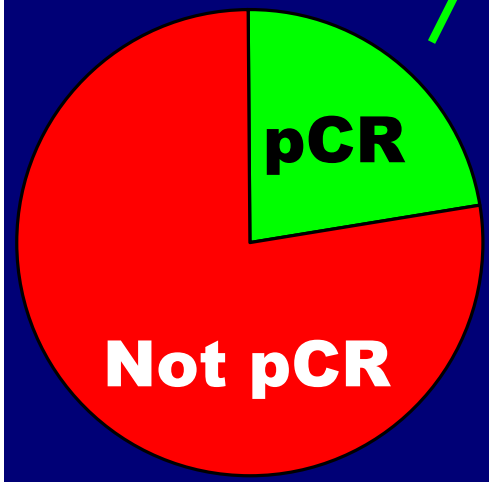
Systemic Therapy After Preoperative Therapy

- 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

Bear, H. D. et al. J Clin Oncol; 24:2019-2027 2006

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

- 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

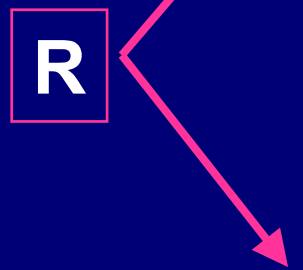
Platform for Research Concepts

- 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

NEO-ADJUVANT TRIAL ADD-ON
NATAN

Surgery for Primary breast cancer within last 3 years
Stage ypT2-4 and / or ypN1-3, and M0
prior preoperative taxane-anthracycline containing chemotherapy

Stratification:
Receptor status
Time since surgery
Age
Center



Observation

Zoledronate 4 mg

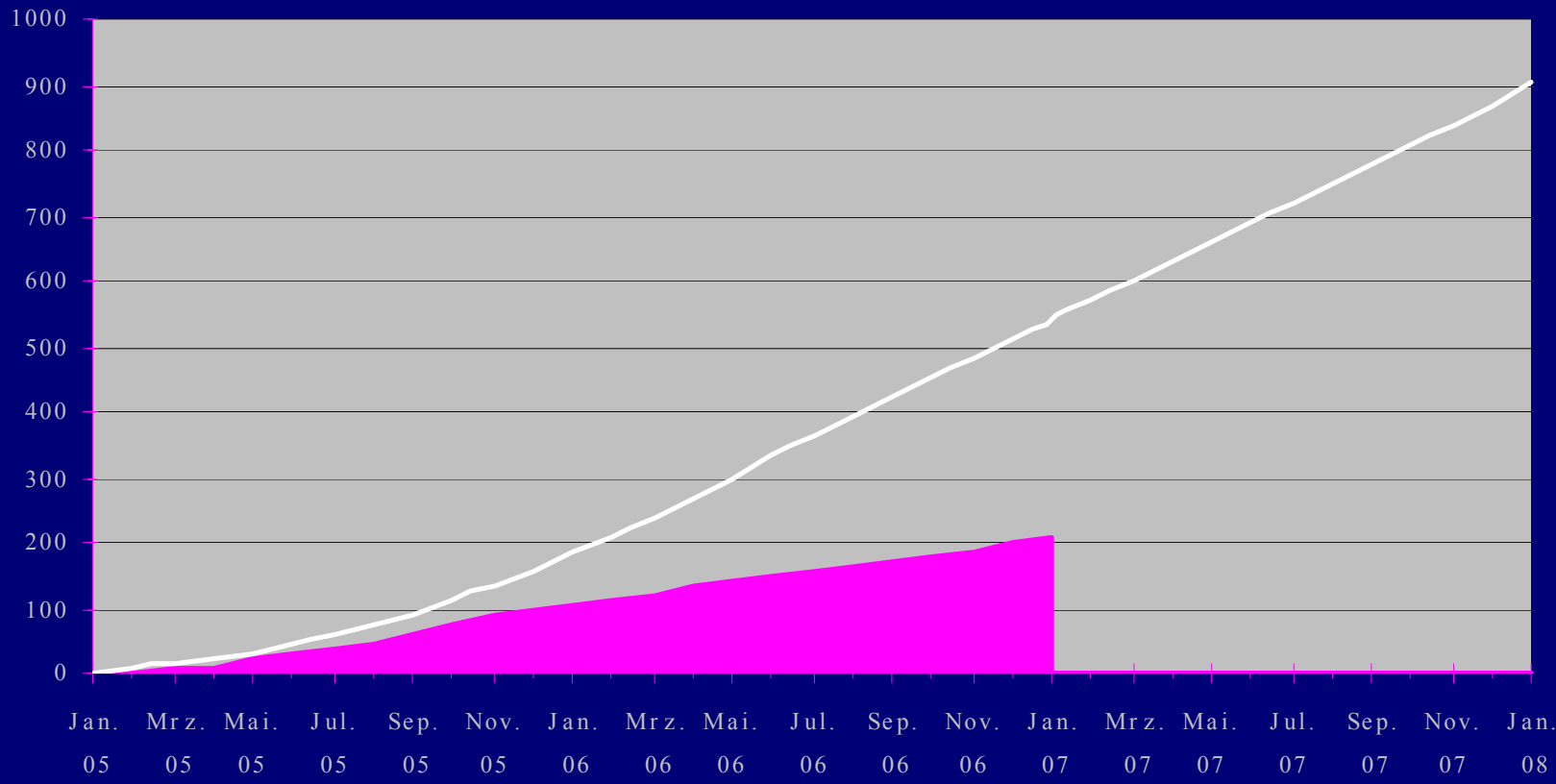
Every 4 weeks for the first 6 doses (year 0 to 0.5)
Every 3 months for 8 doses (year 0.5 – 2.5)
Every 6 months for 5 doses (year 2.5 – 5)

Prior and/or simultanous standard endocrine/antiHer2 treatment

Prior and/or simultaneous radiotherapy

NEO-ADJUVANT TRIAL ADD-ON
NATAN

NaTaN - Recruitment at 01.01.2007
N = 206



DFCI – IU – UCSF - UNC
Feasibility Study of Novel Therapies After Preoperative Chemotherapy

- 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

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

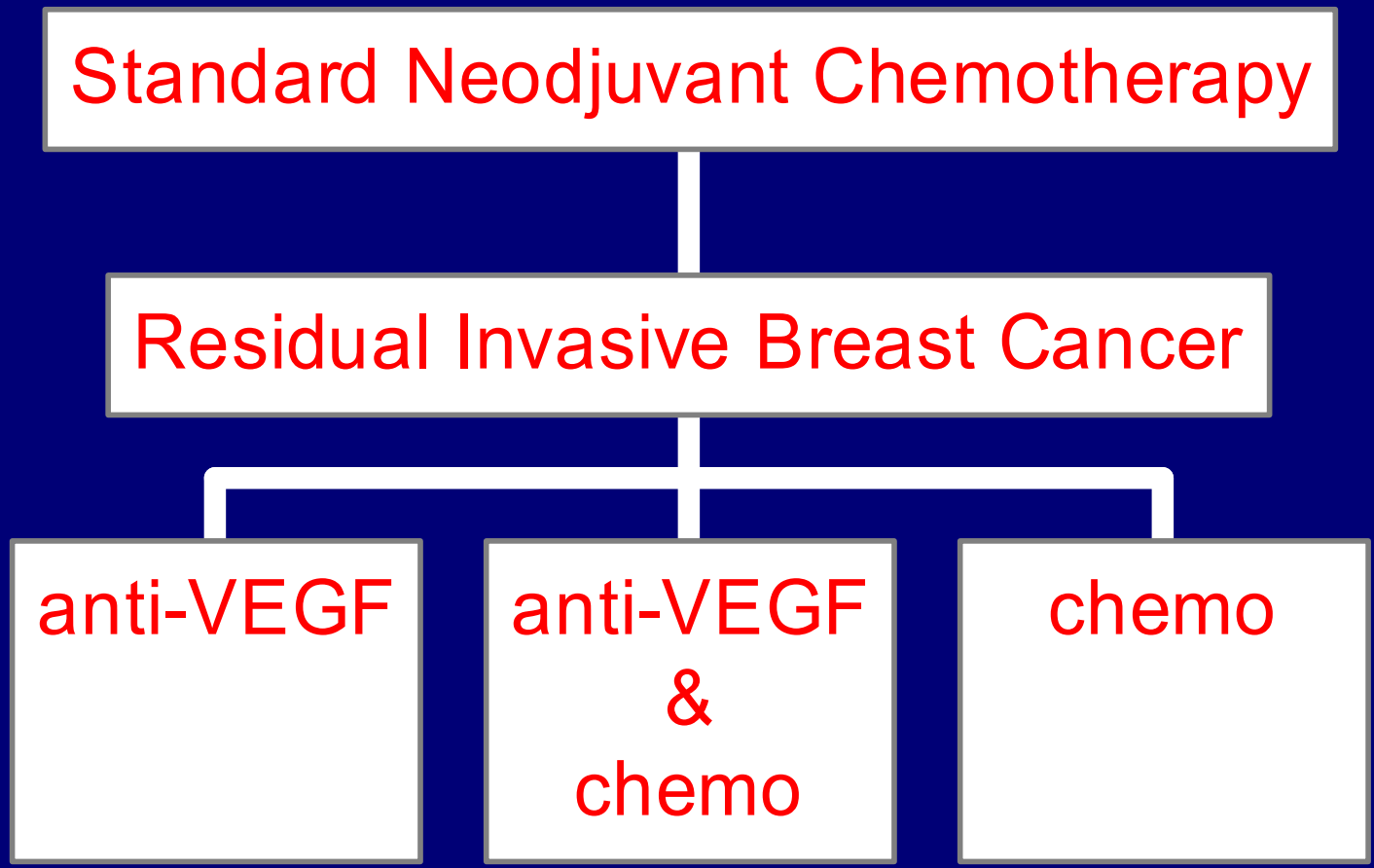
Cohort 3

Capecitabine + bevacizumab

Capecitabine 2000 mg/m^2 days 14 of 21 x 6 cycles

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

Proposed Trial for Post Preoperative Therapy



Summary

- 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