



# Technology Hurdles: Drug Developer Perspective

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Genentech, Inc.

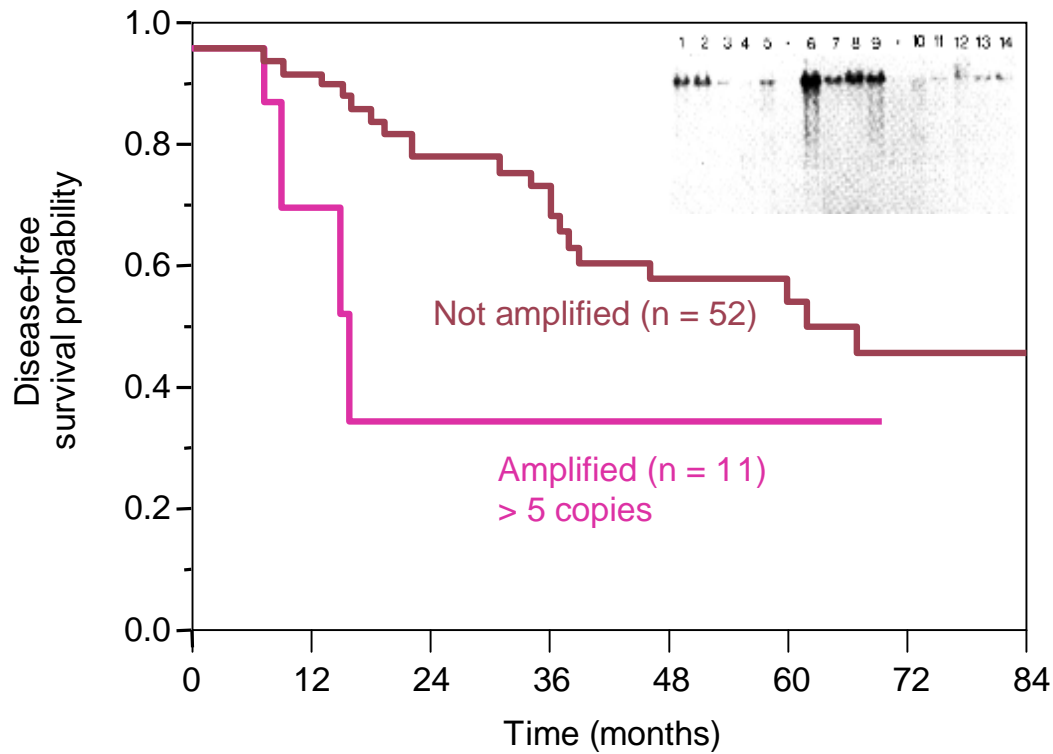
June 8, 2009



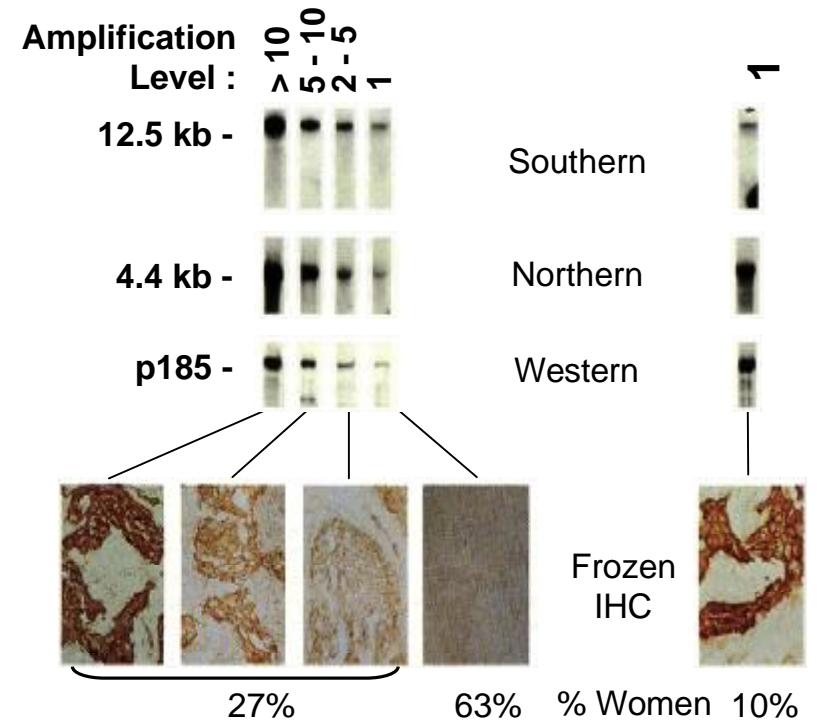
# Diagnostic challenges

- Genentech has been committed to personalized drug development in oncology since Herceptin
- In spite of this commitment, our efforts to improve the lives of individual patients have been challenged by:
  - The differential pace of therapeutic drug development/innovation when compared to diagnostic innovation
    - § Example: Herceptin and HER2 testing
  - The technical challenges of pre-clinical to clinical diagnostic transition
    - § Example: Pertuzumab and HER2 pathway activation
  - The regulatory environment governing the linkage of diagnostic testing and targeted therapy
    - § More about that tomorrow

# The Herceptin program had a viable biomarker from day 1

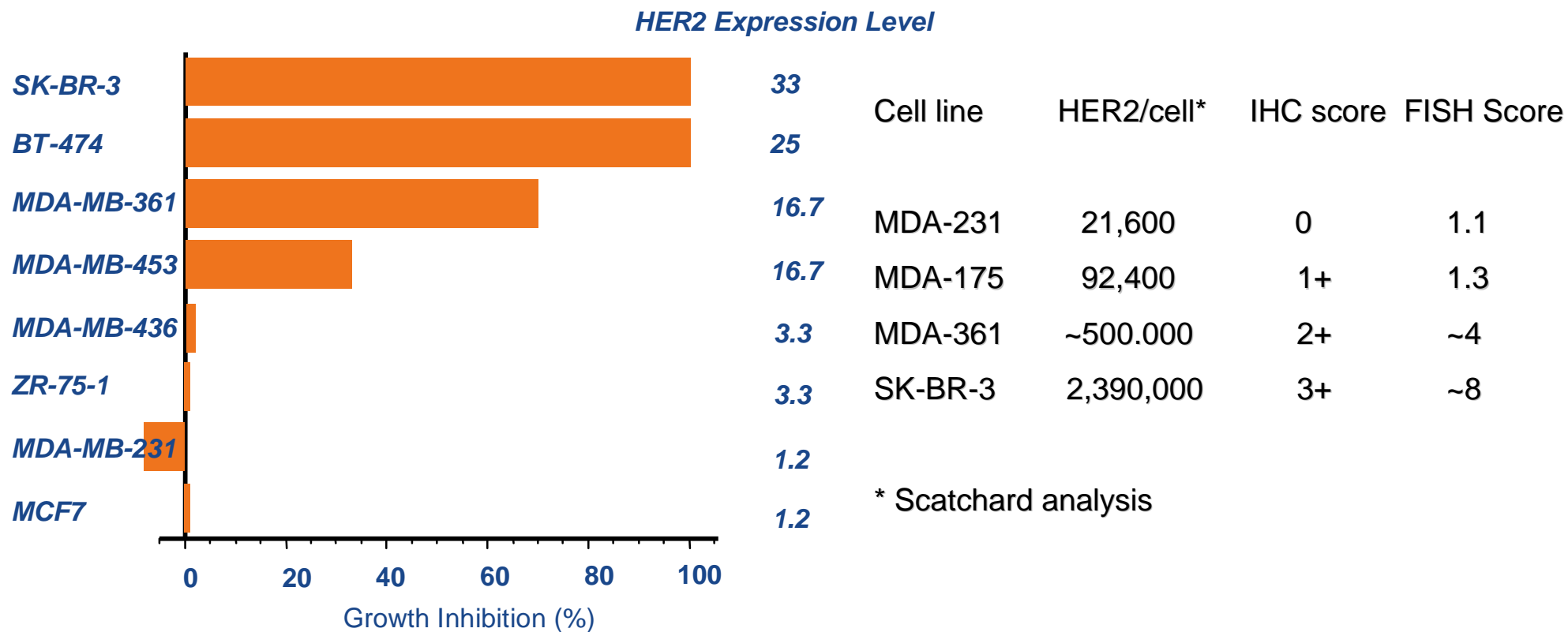


Slamon et al., *Science* 235:177-182, 1987



Slamon et al., *Science* 244: 707-712, 1989

# The Herceptin program had a viable biomarker from day 1



**Antibody Inhibitor (4D5) of Anchorage-Independent Growth Is Related to HER2 Expression Level**

**HER2 IHC score is directly correlated to HER2 density and amplification**

# And.....The Rest is History

VOLUME 344

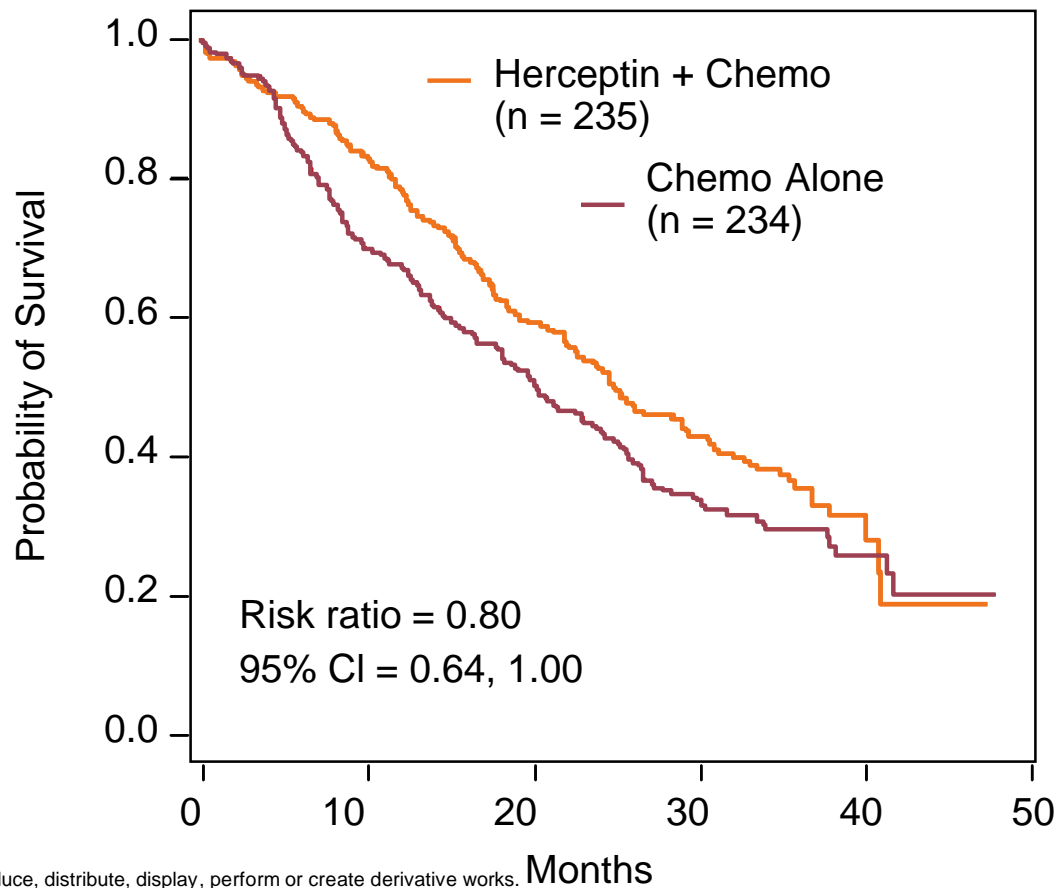
MARCH 15, 2001

NUMBER 11



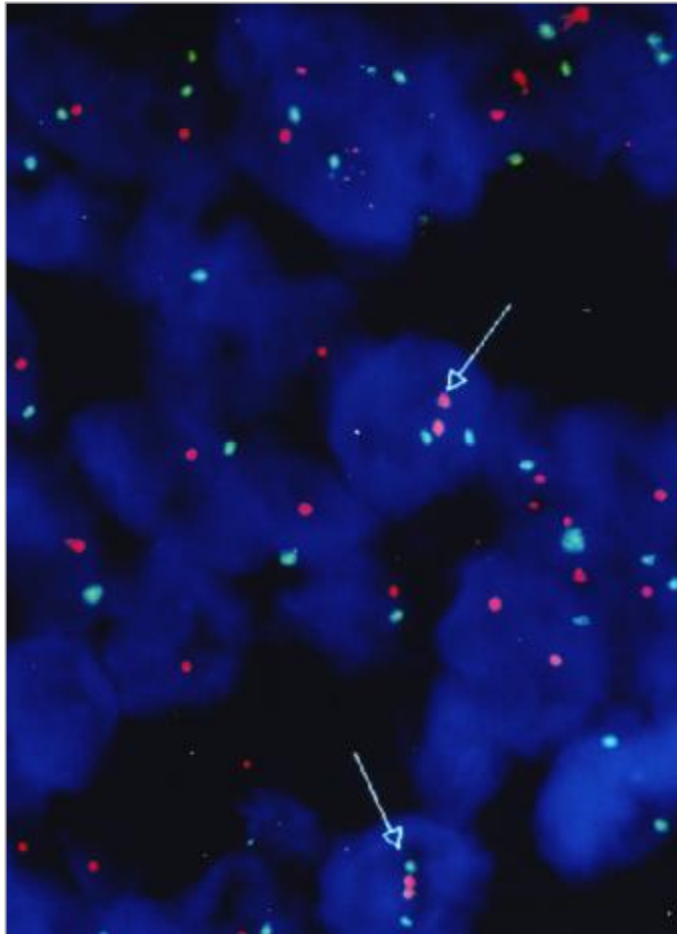
## USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.\*

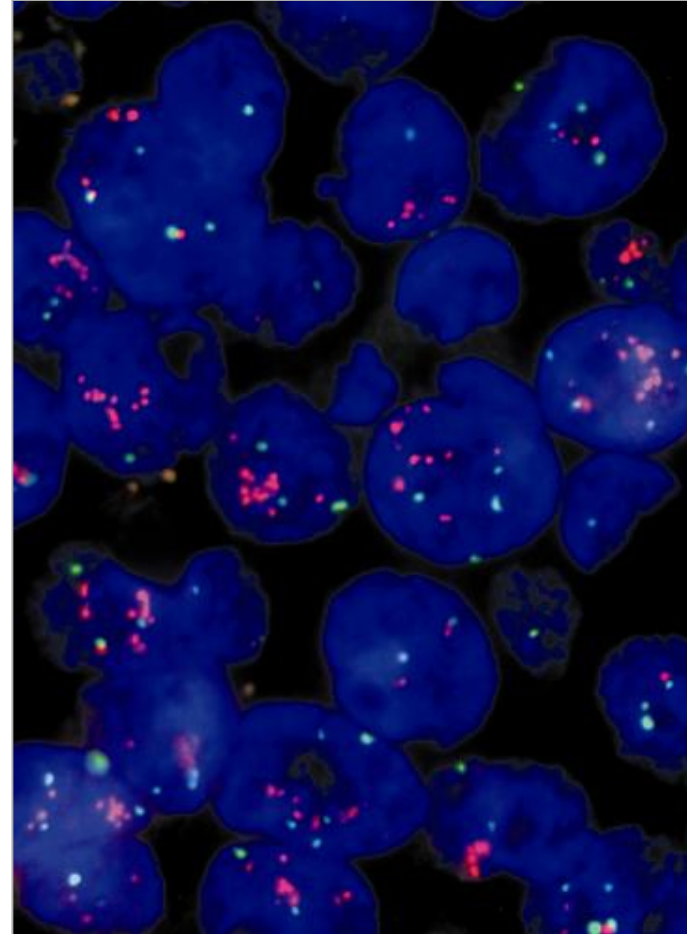


# But not so Fast.....FISH is here!

Orange: HER-2/*neu*  
Green: Chromosome 17 centromere



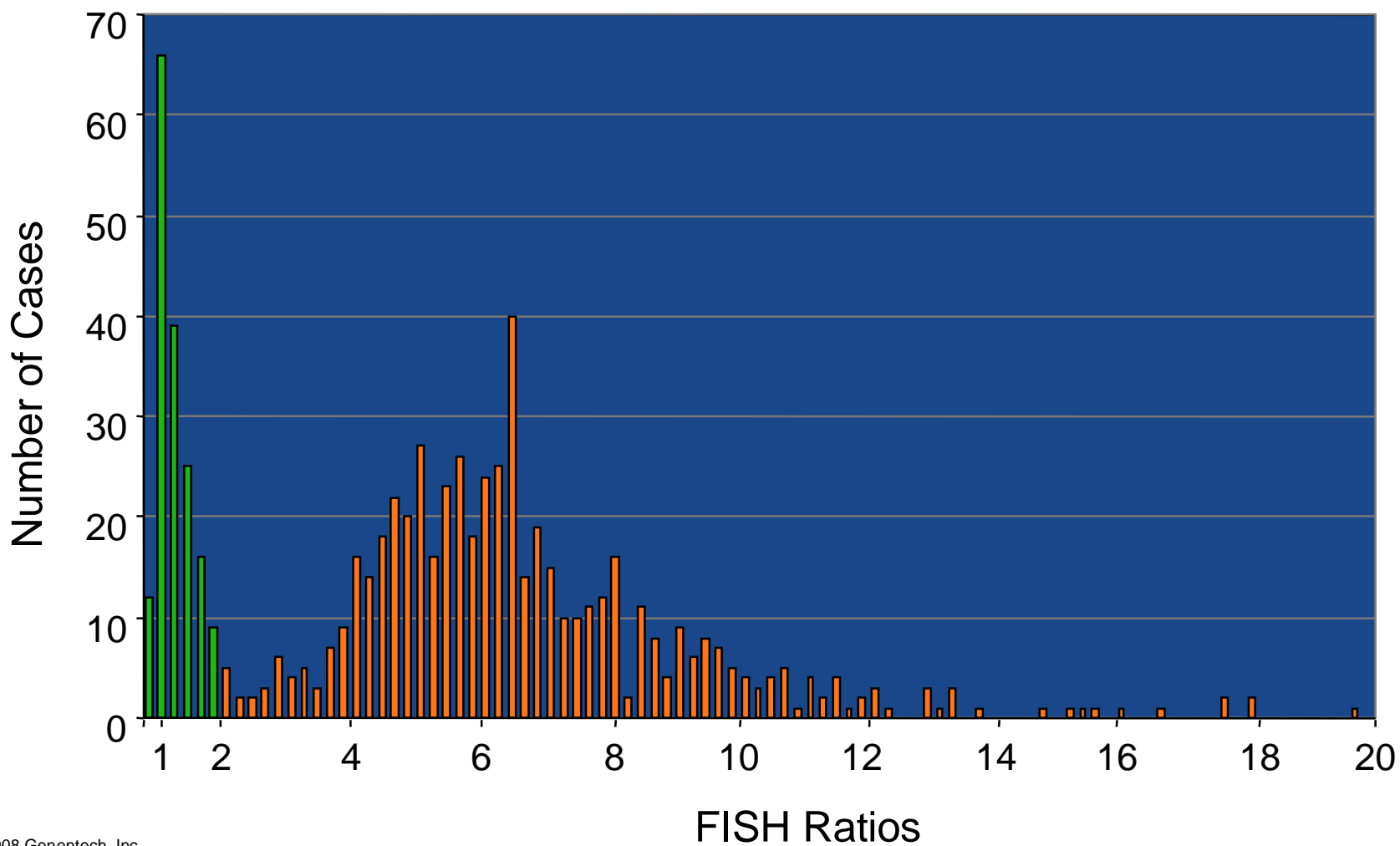
< 2.0 Not Amplified  
(FISH-)



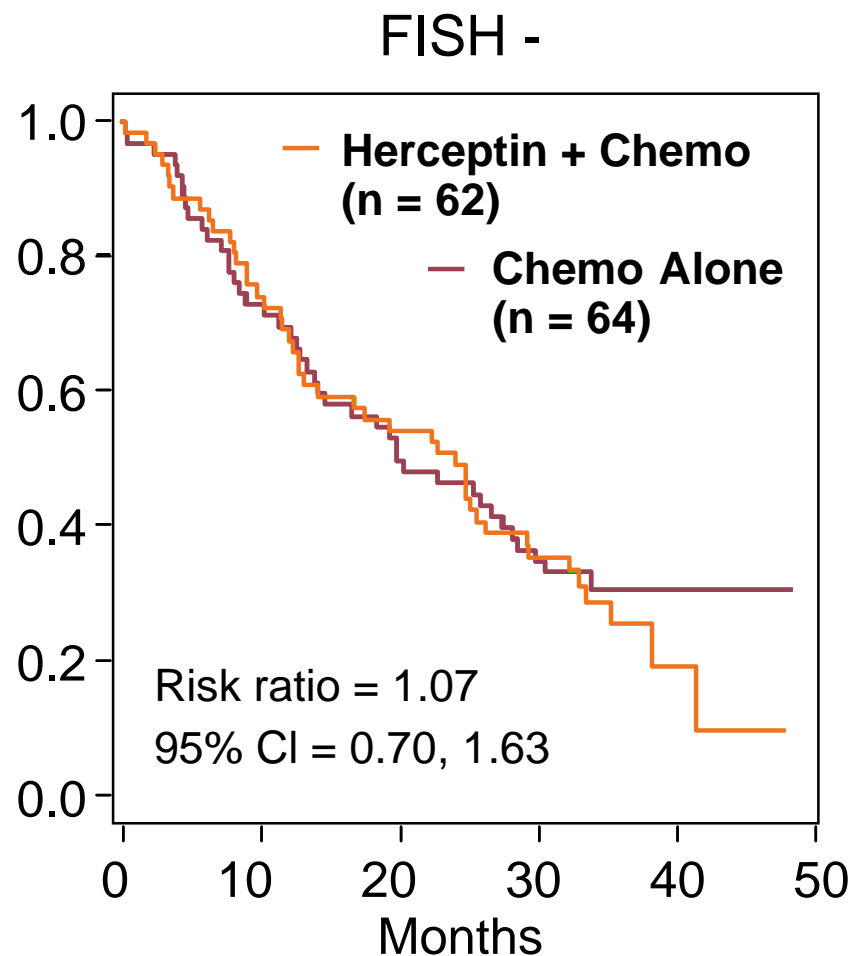
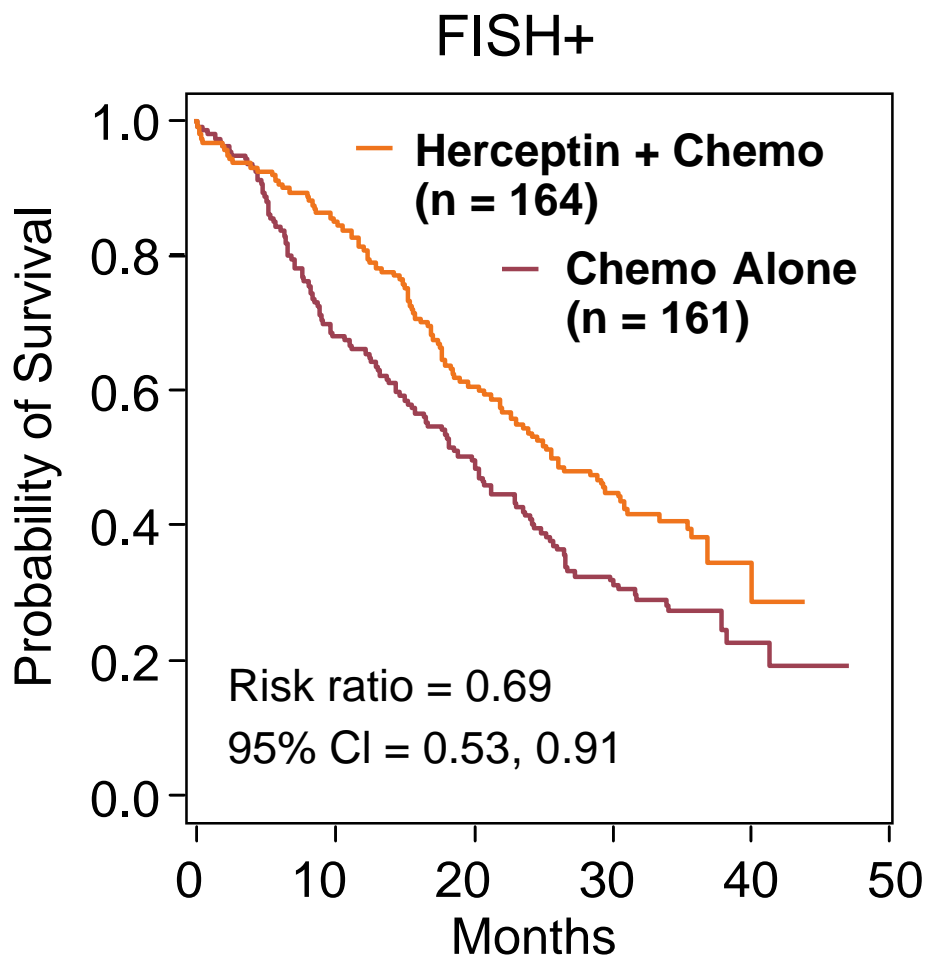
$\geq 2.0$  Amplified  
(FISH+)

# FISH score distribution in the pivotal Herceptin study

*27.9% of study patients were not HER2 amplified*



# Outcome by FISH score in the pivotal Herceptin study



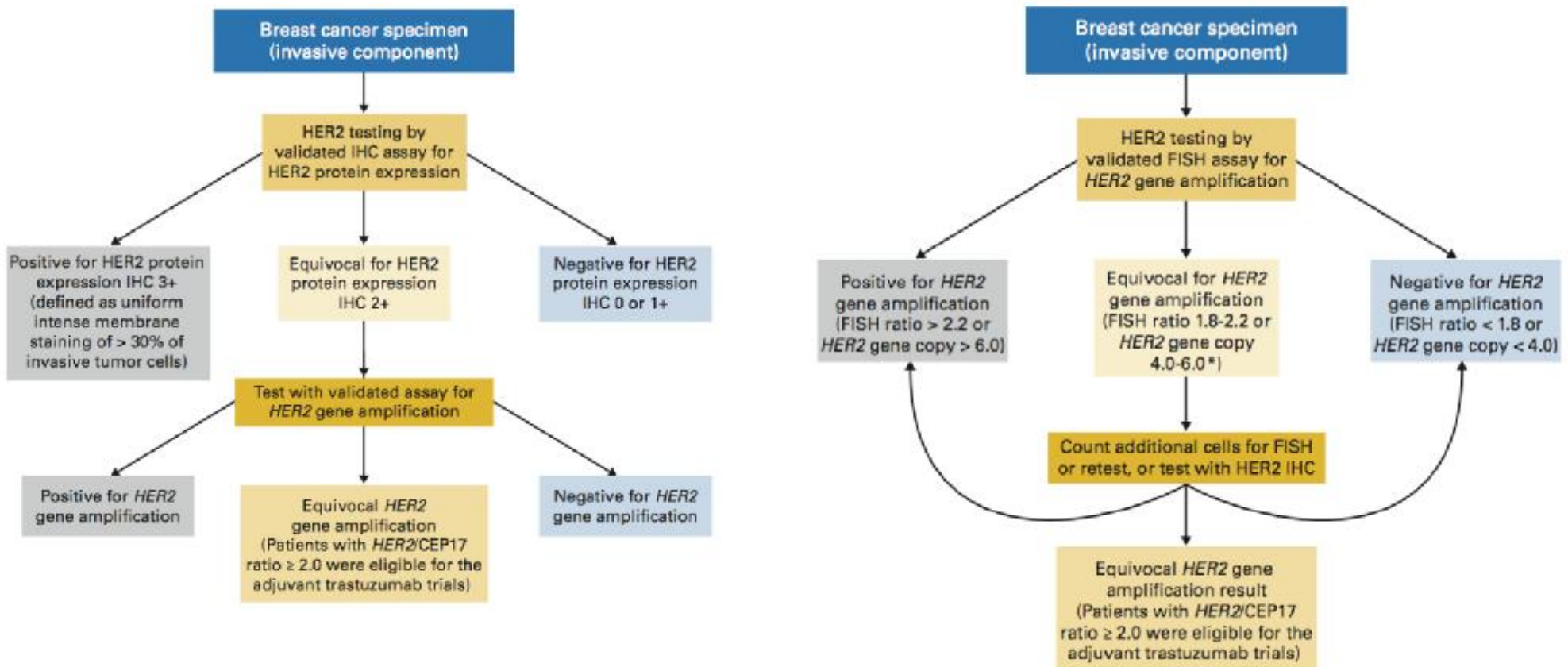


# What did this entail?

- Minimizing loss of informative samples
  - Sufficiently validating novel technology
  - Enabled 96% of patients to be included in outcomes analysis
- Bridging concordance with our FDA approved diagnostic
  - HercepTest vs PathVysion
- Replicating results
  - 799 samples were analyzed in 2 independent laboratories
- Time
  - Project initiated in April 1999, FDA approval April 2002

# Where we are now

(but what about CISH, qRT-PCR, or the next real [or perceived] innovation?)



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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

## American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, Karen L. Hagerty, D. Craig Allred, Richard J. Coe, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila E. Tarab, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler, and Daniel F. Hayes

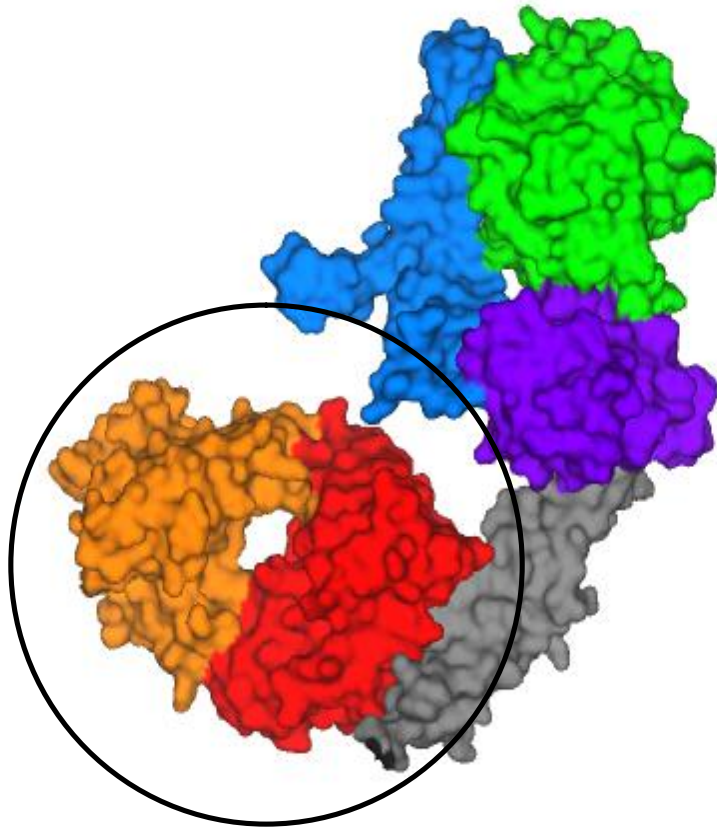
# Pertuzumab

*What do you do when you don't have a viable biomarker from the start?*

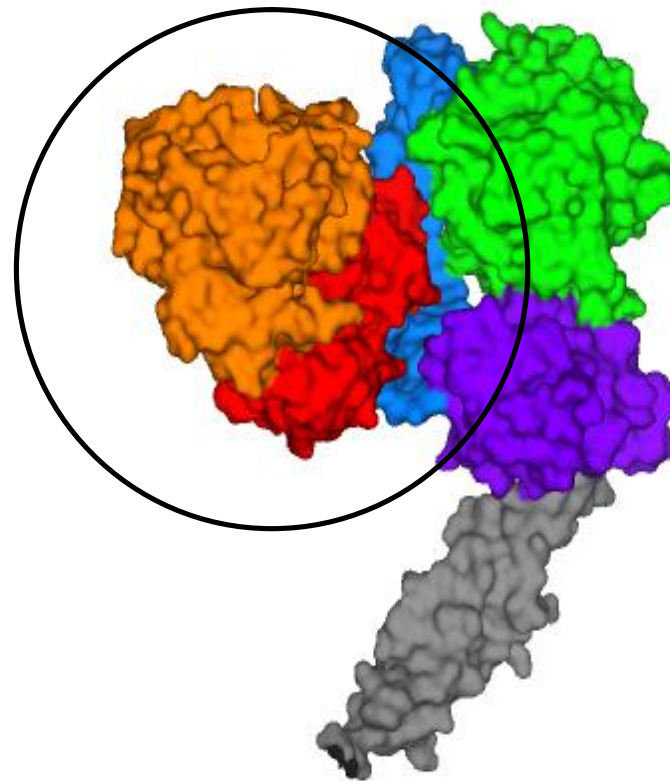
# Trastuzumab vs Pertuzumab

Both anti-HER2 antibodies, but distinct epitopes & MOA's

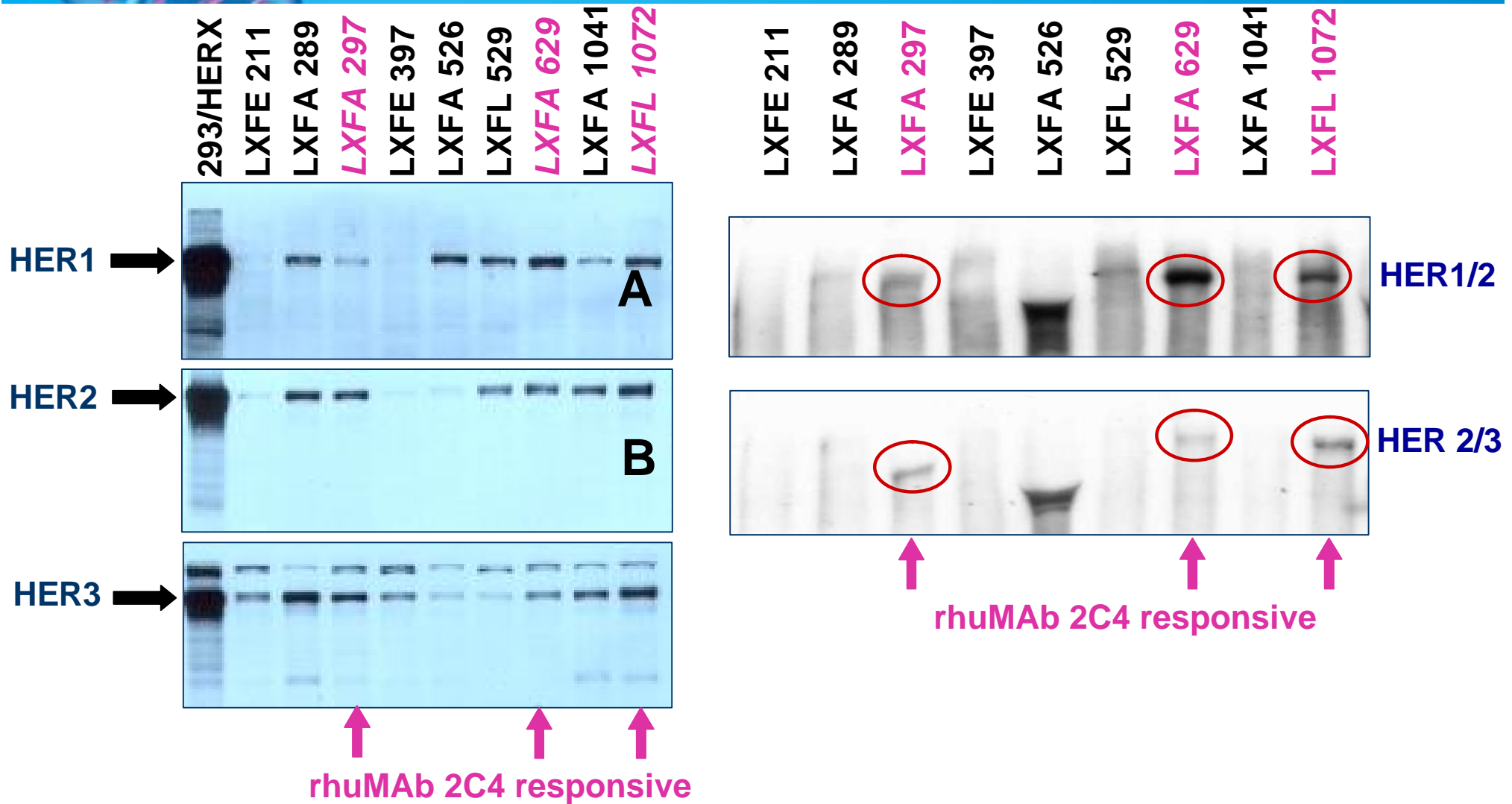
***Trastuzumab***  
***Herceptin***



***Pertuzumab***



# The start of a pertuzumab biomarker



Not associated with HER receptors

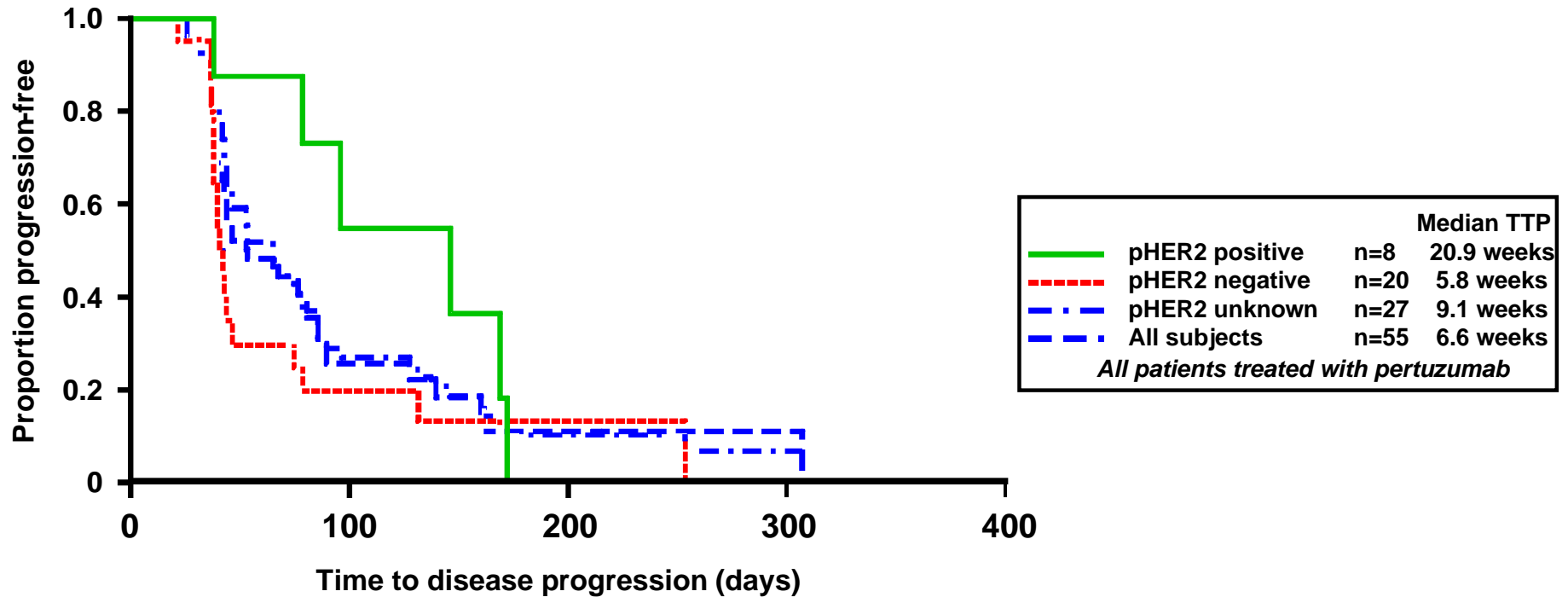
Associated with HER heterodimers



# How do we detect HER2 heterodimers in clinical samples? (harder than you think)

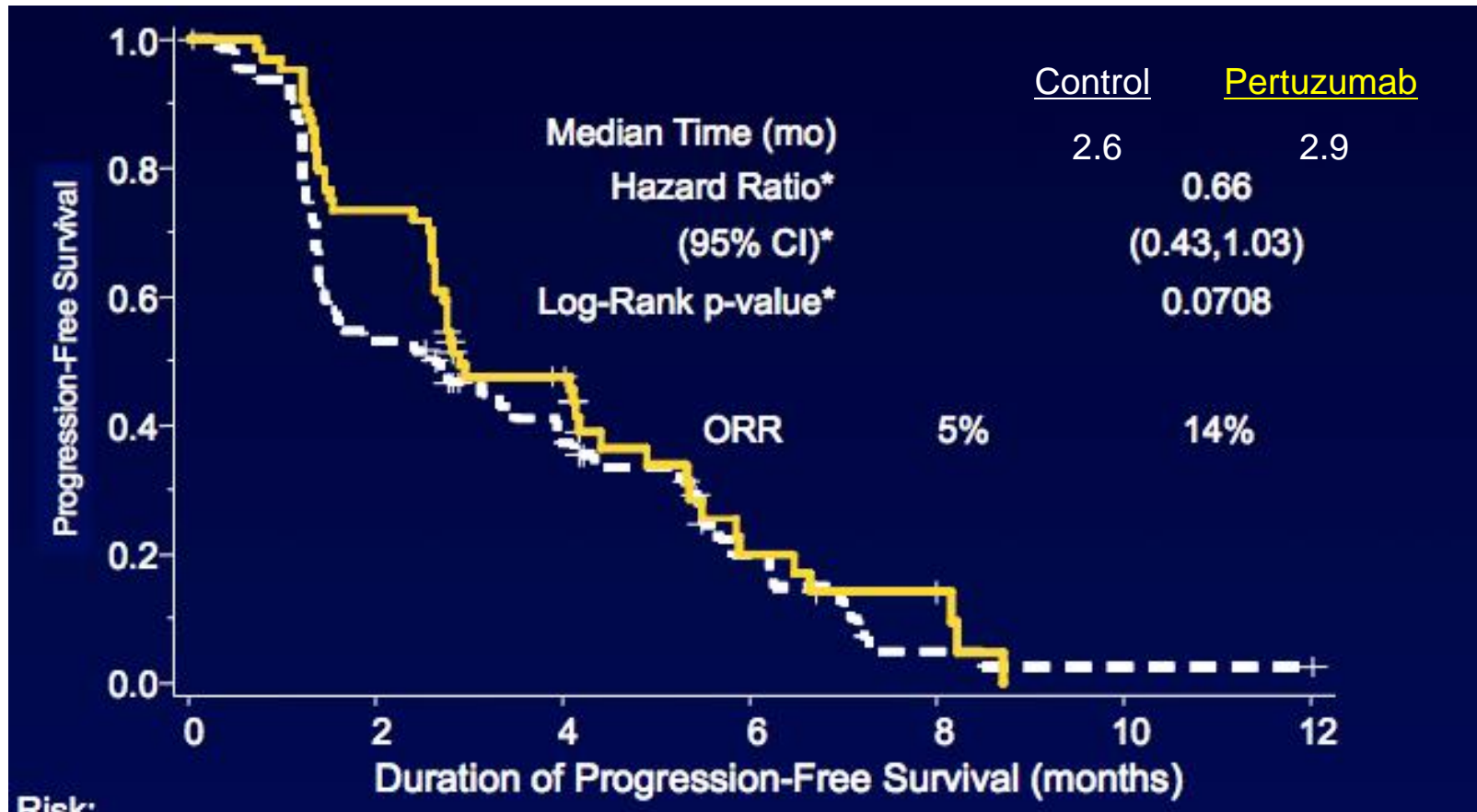
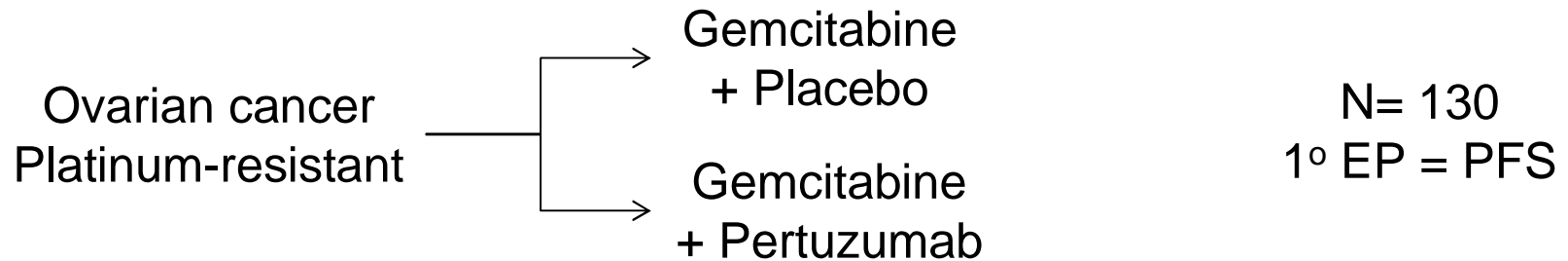
- HER2 activation
  - pHER2
- Directly detect HER dimers
  - Immunoprecipitation and blotting
  - Heterodimer ELISA
  - Development of heterodimer-specific antibody reagents
  - FRET (fluorescence resonance energy transfer)
  - Proximity assays
- Surrogate markers for receptor activation
  - Gene expression profile
  - Proteomic profile
- Downstream regulated gene activity

# The “nearly impossible” clinical experiment



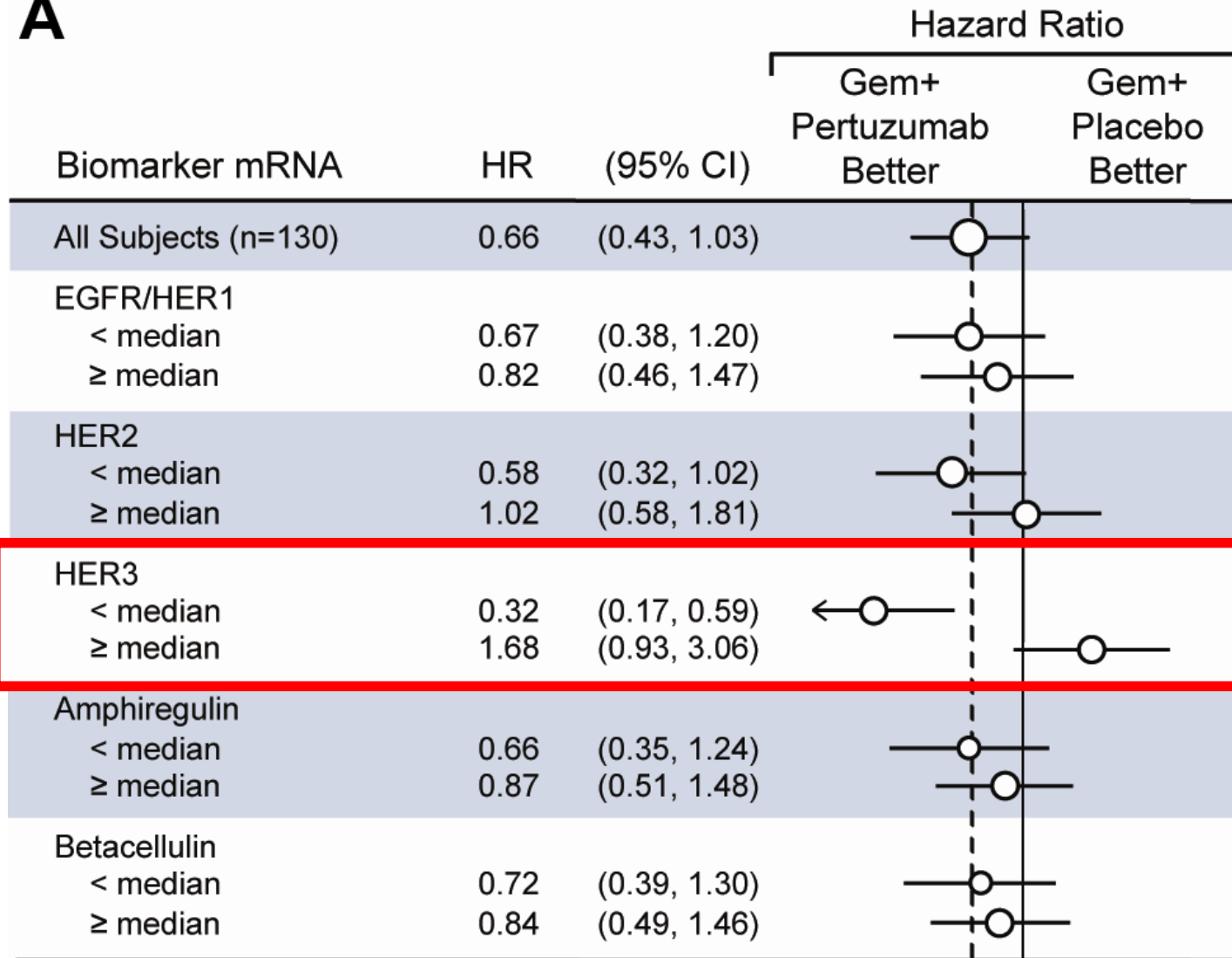
Every patient underwent laparoscopic biopsy for study entry

# Our next trip to the plate.....

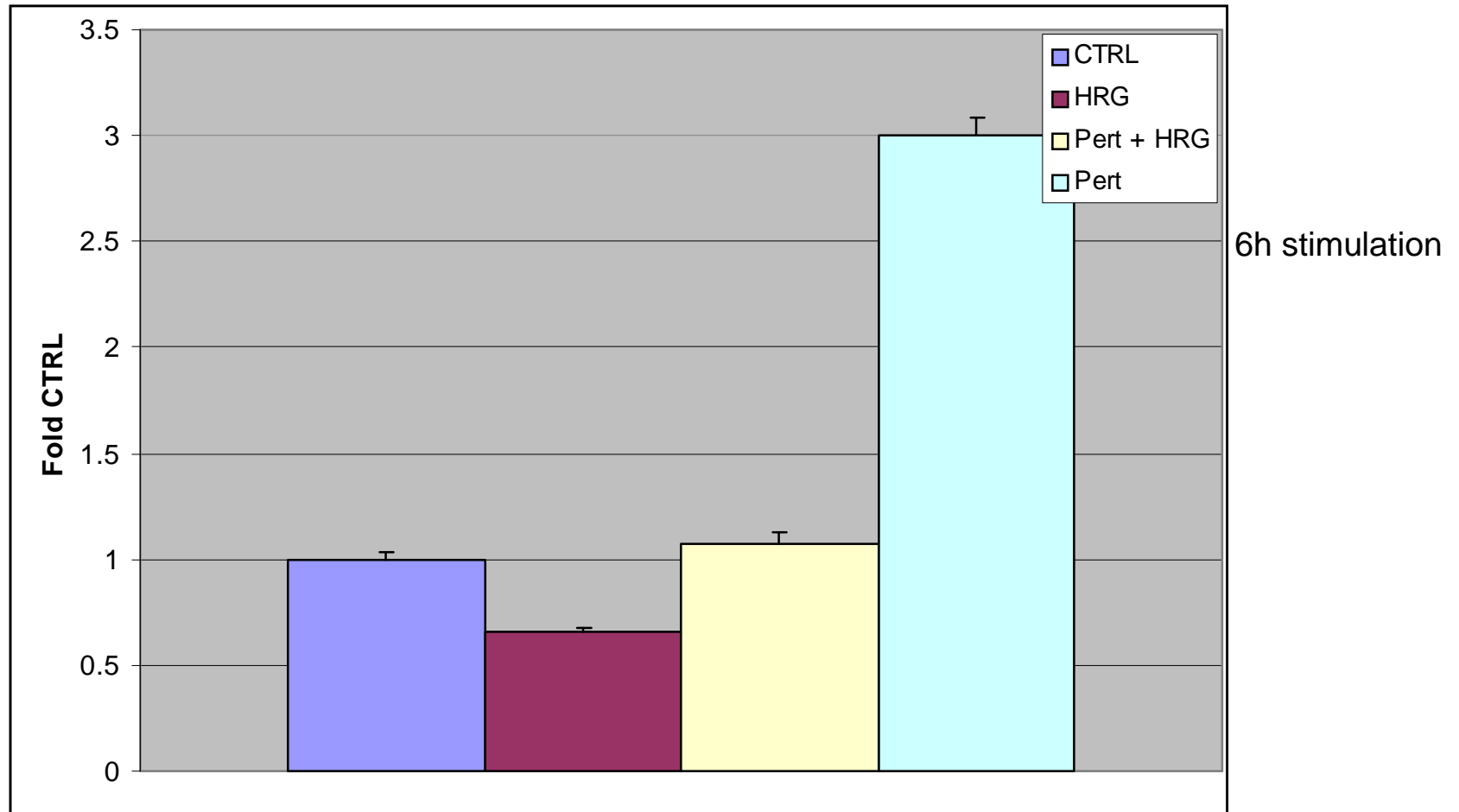


# The ensuing diagnostic interrogation.....

**A**



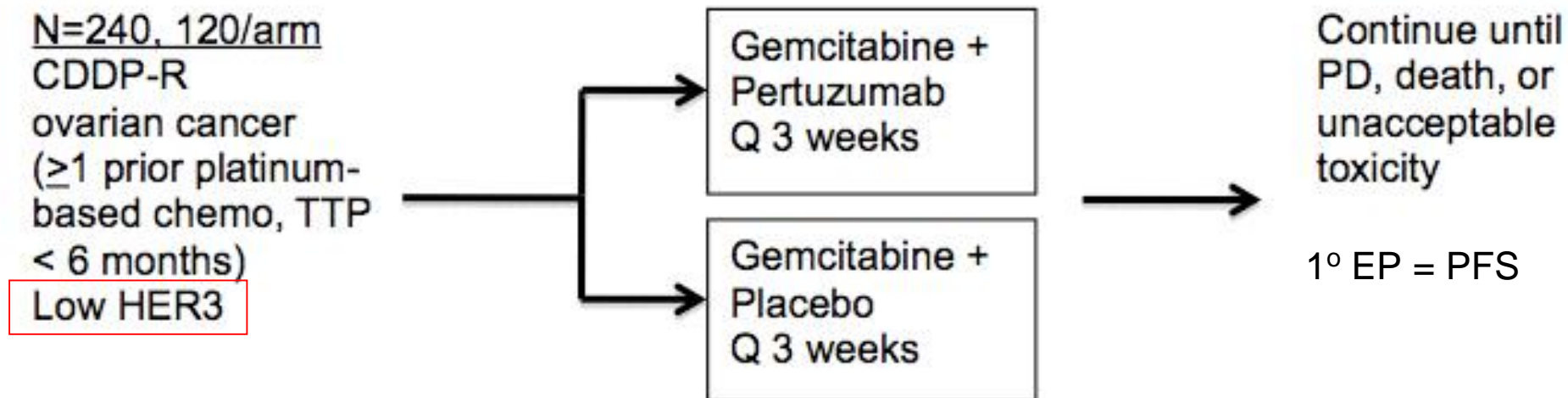
# This is an example of detecting HER2 dimerization via downstream regulated gene activity



6 out of 8 OvCa cell lines down-regulate HER3 mRNA expression after HRG stimulation

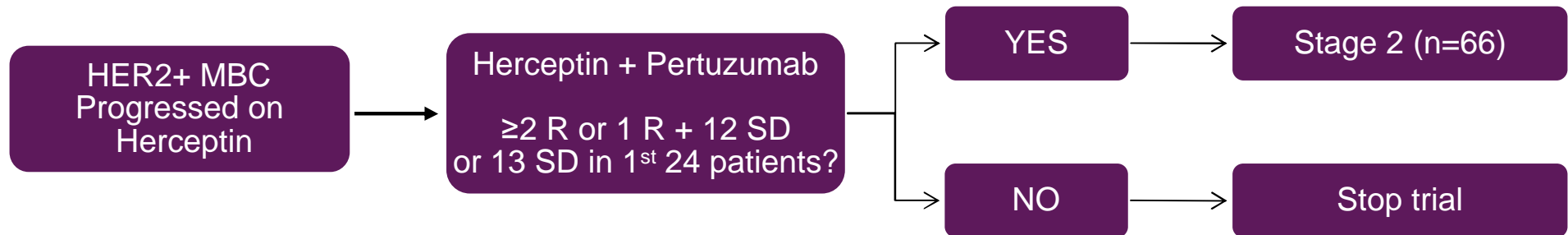
# Our current trip to the plate in ovarian cancer

## Phase 3, Randomized, Blinded Study in Platinum-Resistant Ovarian Cancer



*Looking for a big treatment effect in a small, selected population*

# But what about HER2 amplification?

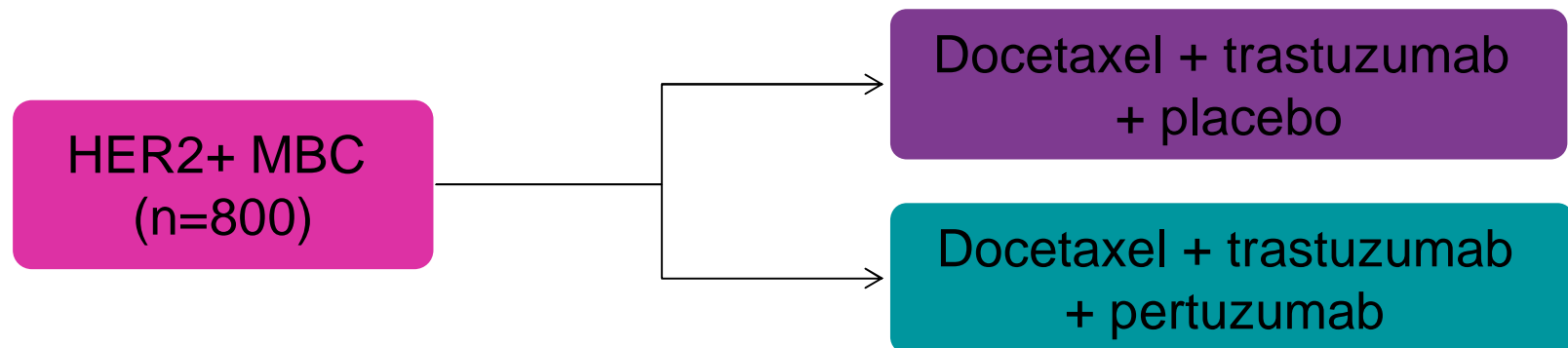


|  | <u>n (%)</u>     |
|--|------------------|
| <b>Complete response<sup>a</sup></b>                           | <b>5 (7.6)</b>   |
| <b>Partial response<sup>a</sup></b>                            | <b>11 (16.7)</b> |
| <b>Stable disease for <sup>≥</sup>8 cycles<br/>(~6 months)</b> | <b>17 (25.8)</b> |
| <b>Objective response rate</b>                                 | <b>16 (24.2)</b> |
| <b>Clinical benefit rate<sup>b</sup></b>                       | <b>33 (50.0)</b> |

Gelmon et al. J Clin Oncol 2008;26(15S): Abstract 1026

# But what about HER2 amplification?

## CLEOPATRA



**An international Phase III randomized, double-blind, placebo-controlled study (approximately 250 sites worldwide)**

### **Enrollment stratified by:**

- n** Prior treatment for breast cancer
- n** Geographic region of enrollment

### **Endpoints:**

- n** PFS and OS
- n** Quality of life
- n** Biomarker analysis



# Conclusions

- In retrospect, Herceptin was the exception, not the rule
  - *This is a lot harder than we thought!*
- A major technologic hurdle remains the availability of appropriately processed tissue for exploratory biomarker assessments
  - *FFPE material is a bad platform....most of the time*



# Our Touchstone: The Diagnostic Iceberg

