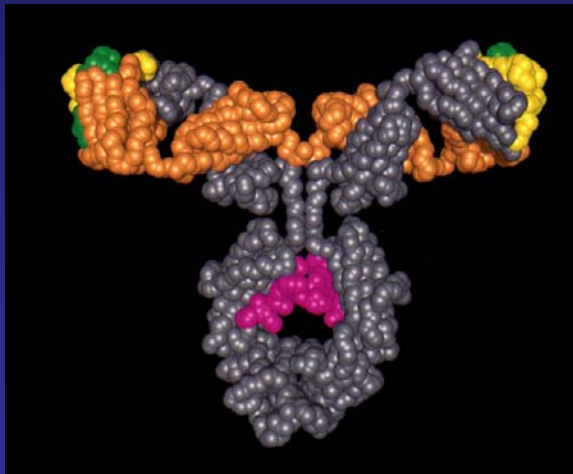


# HERCEPTIN® (Trastuzumab)

*A Real World Example of  
Pharmacogenomics –  
Maximizing Patient Benefit*



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Sr. Manager, Regulatory Affairs  
Genentech, Inc.  
July 29, 2004*



# Targeting HER2 in Breast Cancer with Monoclonal Antibodies

Herceptin Product Development History

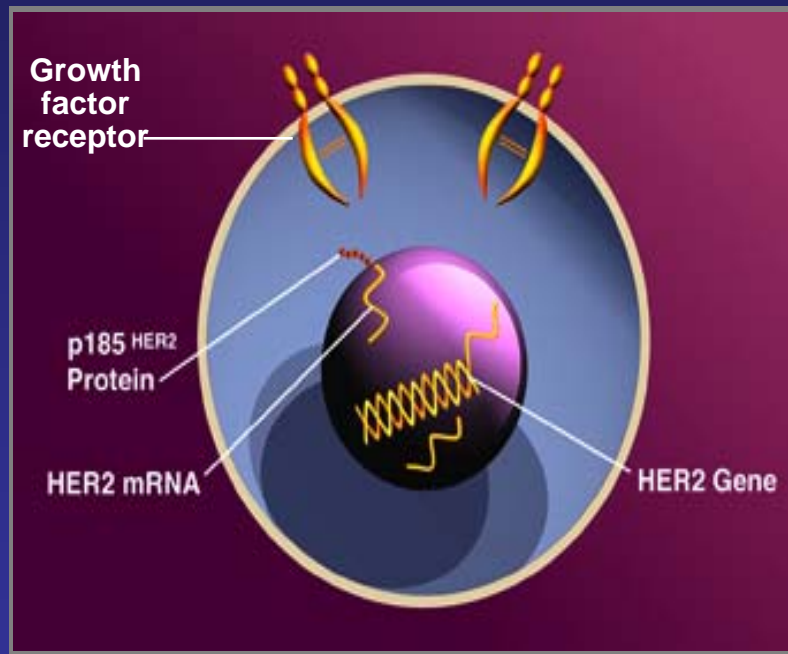
HER2 Testing and Patient Selection

Pre-approval Diagnostic Strategy

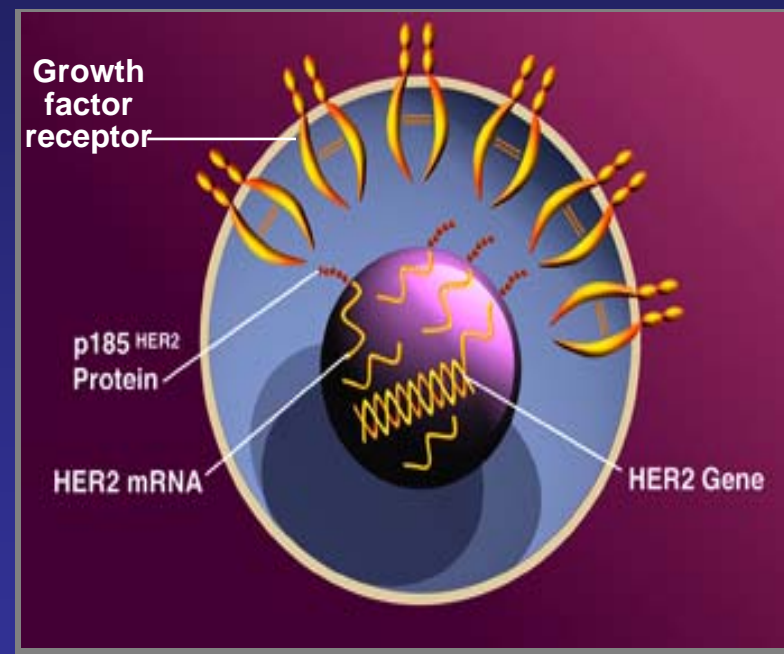
Post-approval Diagnostic Development

# HER2 Protein Overexpression

## Normal



## Overexpressing



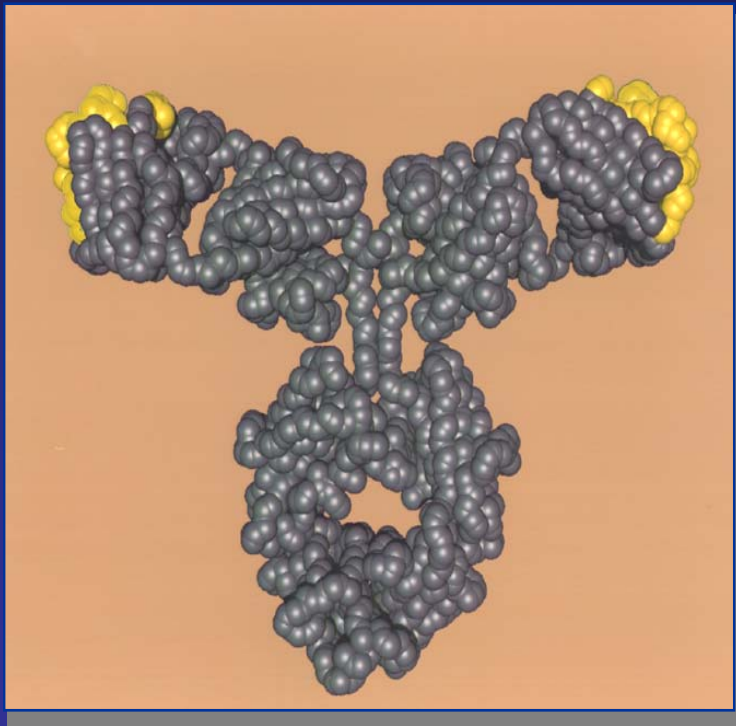
# HER2 in Breast Cancer

- ◆ Approximately 20% to 25% of breast cancers are HER2 positive
  - ➔ Tumors that are HER2 overexpressing
    - Metastasize faster
    - Respond differently to treatment
- ◆ HER2 protein overexpression associated with poor prognosis

# Blocking HER2 with Monoclonal Antibodies

- ◆ Anti-HER2 monoclonal antibodies inhibit
  - In vitro proliferation of HER2 protein overexpressing human tumor cells
  - In vivo tumor growth of human breast cancer xenografts in nude mice

# Humanized Anti-HER2 Antibody



- ◆ Targets HER2 oncoprotein
- ◆ High affinity ( $K_d = 5\text{nM}$ ) and specificity
- ◆ 95% human, 5% murine
  - Decreased potential for immunogenicity
  - Increased potential for recruiting immune effector mechanisms

Carter et al, 1992; Park et al, 1993; Slamon et al, 1987; Genentech, data on file

# Targeting HER2 in Breast Cancer with Monoclonal Antibodies



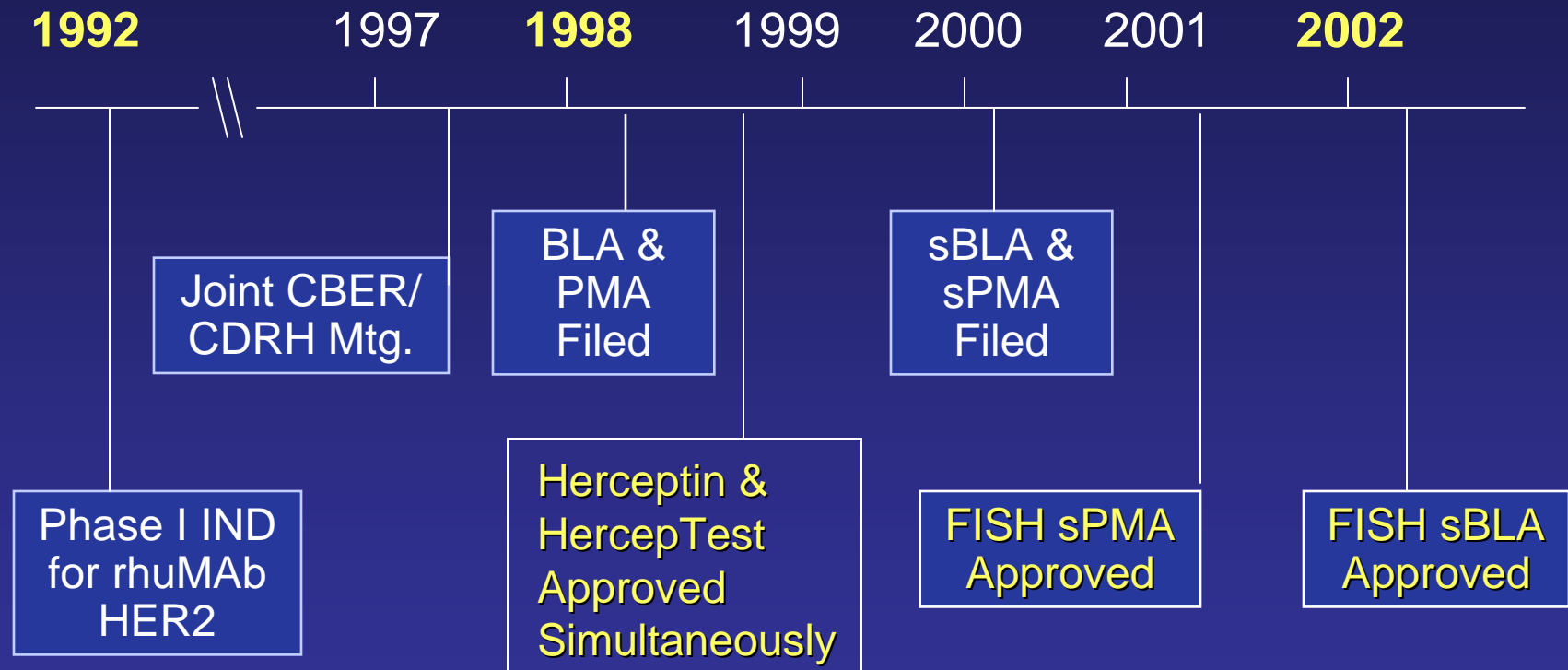
## **Herceptin Product Development History**

HER2 Testing and Patient Selection

Pre-approval Diagnostic Strategy

Post-approval Diagnostic Development

# Product Development History



Targeting HER2 in Breast Cancer with  
Monoclonal Antibodies

Herceptin Product Development History

 **HER2 Testing and Patient Selection**

Pre-approval Diagnostic Strategy

Post-approval Diagnostic Development

# Clinical Trials Assay (CTA)

- 2+ or 3+ protein overexpression required for study entry
- ◆ Standardized immunohistochemistry (IHC) assay
- ◆ Developed at Genentech for Phase I-III clinical trials
- ◆ All testing performed at a central core laboratory (LabCorp)

# Pivotal Trial Results

- ◆ Efficacy of C + H vs. C alone:
  - prolonged time to progression (7.2 vs. 4.5 mo.)
  - improved response rates (45% vs. 29%)
  - increased duration of response (8.3 vs. 5.8 mo.)
- ◆ Longer follow-up:
  - **25%** increase in overall survival

Targeting HER2 in Breast Cancer with  
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Herceptin Product Development History

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 **Pre-approval Diagnostic Strategy**

Post-approval Diagnostic Development

# Rationale for Diagnostic Strategy

- ◆ Clinical trial assay (CTA) defined eligibility for Herceptin trials
- ◆ CTA establishes a de facto standard
- ◆ CTA was not commercially viable

# Rx/Dx Regulatory Process

- ◆ Require commercially available IVD HER2 test for marketing of Herceptin
- ◆ Genentech partners with DAKO to develop a commercially available IHC kit
- ◆ CDRH/CBER Joint Meeting defines process for approval of the Rx/Dx combination

# Concordance of the HercepTest to the Clinical Trial Assay

		Clinical Trial Assay		
		+	-	Total
HercepTest	+	216	59	275
	-	58	215	273
	Total	274	274	548

Concordance = **79%** (76%-82%)

# Concurrent Approval Timeline

## CBER Process

- Genentech files BLA  
May 1, 1998 for  
Herceptin
- Positive ODAC Mtg  
Sept 2, 1998 with  
representation from  
CDRH

## CDRH Process

- DAKO files PMA  
May 15, 1998 for IVD
- Positive Device Panel  
Mtg Sept 4, 1998 with  
representation from  
CBER

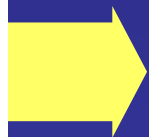
Applications receive simultaneous approval on  
September 25, 1998

Targeting HER2 in Breast Cancer with  
Monoclonal Antibodies

Herceptin Product Development History

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Pre-approval Diagnostic Strategy



**Post-approval Diagnostic Development**

# Rationale for Exploring FISH

- ◆ Response to the medical community
- ◆ Post approval commitment to explore alternative methods for patient selection
- ➔ Data suggesting that FISH may provide improved accuracy for selecting patients for Herceptin therapy

# Fluorescence in situ Hybridization

- ◆ detects HER2 gene amplification
- ◆ can be performed on FFPE sections
- ◆ allows single cell evaluation

specificity = 100%  
sensitivity = 96-98%

Kallioniemi O, *PNAS* 89:5321-25, 1992  
Pauletti G, *Oncogene* 13:63-72, 1996

# FISH/CTA Concordance

		CTA				
		0	1+	2+	3+	
FISH	-	<b>207</b>	<b>28</b>	67	21	
	+	7	2	<b>21</b>	<b>176</b>	
		3%	7%	24%	89%	529

FISH+ = HER2:CEP17 signal ratio  $\geq 2$

Concordance = **82%** (79-85%)

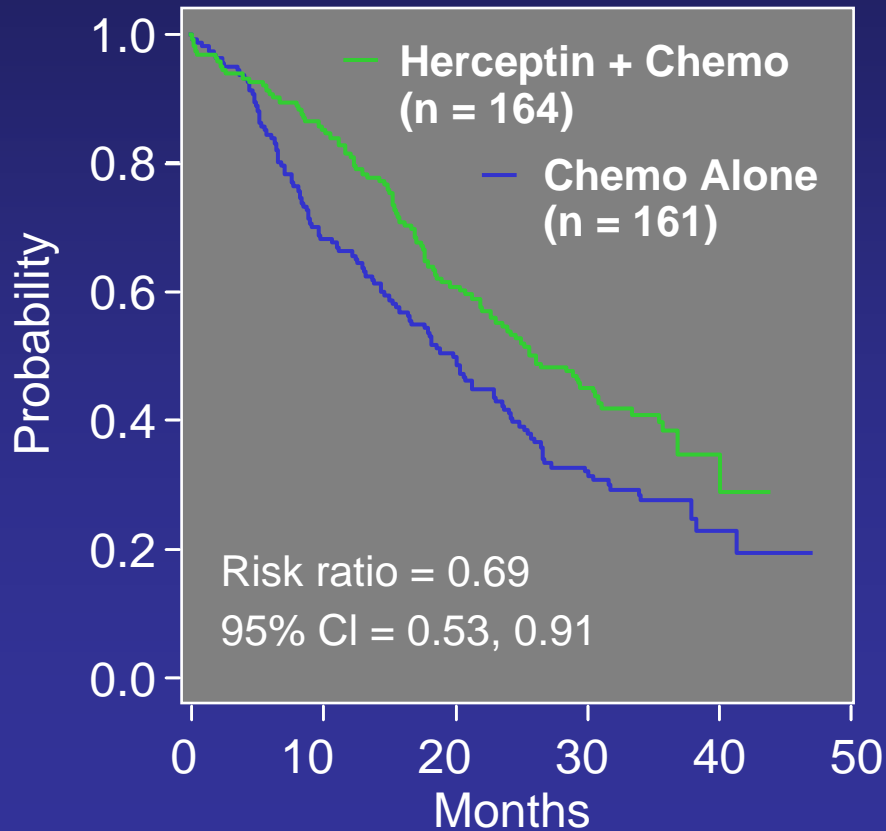
# FISH Clinical Outcome Study

- ◆ We partnered with Vysis using the approved PathVysion Assay
- ◆ Link clinical outcome with FISH status from 3 pivotal Herceptin trials
- ◆ Additional clinical material from 96% of the total patient population
- ◆ Cut sections stored between 2.5 and 4.5 years

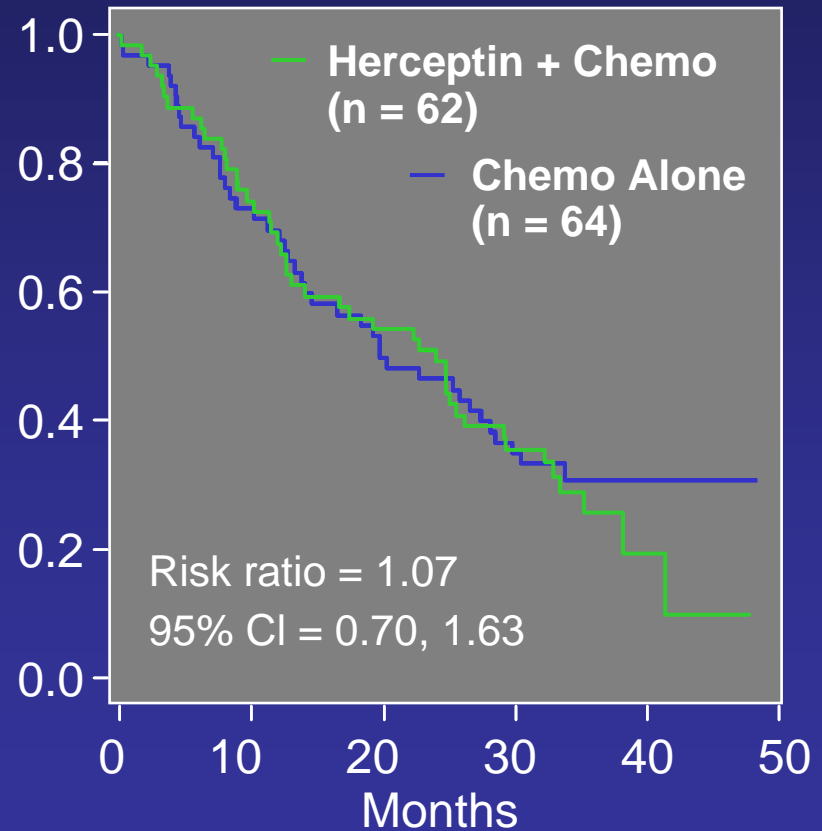
# Survival

## Chemotherapy +/- Herceptin, 1st line MBC

FISH+



FISH -



# The FISH+ population:

- ◆ Is highly correlative with the IHC+ population
- ◆ Demonstrate clear benefit from Herceptin
- ◆ Demonstrate no new safety signals
- ◆ Represents a reduction in the Herceptin eligible patient population
- ➔ Eliminates patients who do not appear to benefit from treatment

# Rx/Dx Regulatory Process

- ◆ Genentech partners with Vysis to expand therapeutic label to include FISH testing as a method for patient selection
- ◆ CDRH/CBER Joint Meeting defines process for approval of the Rx/Dx combination

# Concurrent Approval Timeline

## CBER Process

- Genentech files sBLA  
March 30, 2001 for  
Herceptin
- Positive ODAC Mtg  
Dec 5, 2001
- sBLA approved  
Aug 28, 2002

## CDRH Process

- Vysis files PMA  
March 30, 2001 for  
IVD
- No Device Panel Mtg.
- PMA approved  
Dec 31, 2001

# Importance of Patient Selection

- ◆ Herceptin targets a genetically determined disease
- Herceptin demonstrates that pharmacogenomics can maximize patient benefit versus risk
- ◆ Preclinical and clinical data suggest no evidence of benefit in HER2 negative

# Lessons Learned

- The diagnostic is absolutely **critical** -  
Early use of a scalable test is essential
- ◆ Availability of tumor blocks and consent from patients enrolled in clinical trials imperative
- ◆ Internal FDA advocacy important
- ◆ Early and often FDA communications with involvement from both Centers