



***American Enterprise Institute for
Public Policy Research***

Clinical Trial Design

**Gwen Fyfe, M.D.
Genentech, Inc.**

March 13, 2008

The Problem Statement:

How can we more 'quickly' determine whether experimental therapeutics provide benefit to patients in the United States?



Why “Quick “ is getting harder and harder...

■ The drugs

- There are many approved cancer treatments
- Increasing numbers of oncology agents in development
- Off label use of multiple active chemotherapies and regimens

■ The patients

- The same or fewer patients are available for clinical trials in USA
- Patients are living longer (good), but achieving survival improvement is more difficult and takes much longer
- Receiving more lines of treatment (complicates survival endpoint)

■ Because of these advances, clinical “benefit” harder to show

- Endpoints, trial size, complications with targeted agents and molecular subsets

If our goal is to understand risk & benefit for patients in the USA health care system, something must change.



More Drugs in Development...

Chemotherapies approved for Breast Cancer Treatment in the USA

Older Drugs (before 1975)

- Methotrexate
- Cyclophosphamide
- Thiotepa
- Vinblastine
- 5-Fluorouracil
- Doxorubicin

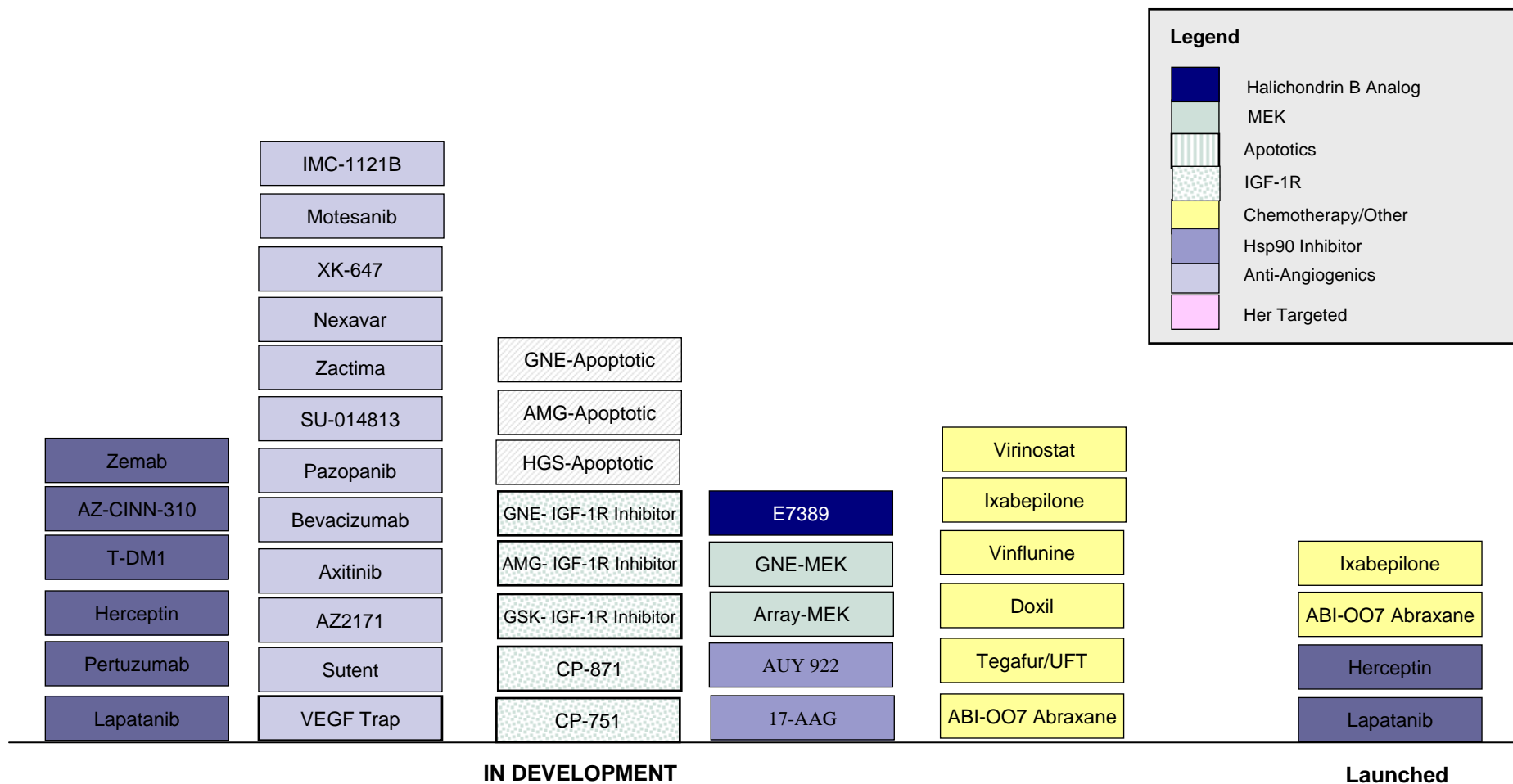
Newer Drugs (after 1993)

- Paclitaxel
- Docetaxel
- Trastuzumab
- Capecitabine
- Capecitabine + Docetaxel
- Abraxane
- Lapatinib
- Ixabepilone

Commonly Used Regimens for the Treatment of Metastatic Breast Cancer

First-Line Options (Chemotherapy)	Subsequent Lines (Chemotherapy)	Hormonal and Targeted Therapy
Docetaxel	Gemcitabine	Trastuzumab
Taxol	Vinorelbine	Lapatinib
Abraxane	Taxol	Exemestane
AC (Doxo, CTX)	Capecitabine	Anastrozole
EC (EpiRub, CTX)	Abraxane	Fulvestrant
Capecitabine	Docetaxel	Letrozole
Docetaxel/Capecitabine (XD)	5-FU	TAM
FAC (5FU, Doxo, CTX)	CMF	
FEC (5FU, EpiRub, CTX)	Doxil	
Carboplatin/Taxol (CT)	Carboplatin	
CMF (CTX, MTX, 5FU)	Ixempra	
Taxol/Gemcitabine		
AT (Doxo, Taxol)		

Drugs in Development for the Treatment of Metastatic Breast Cancer



Sources: Clinicaltrials.gov



**The same (or fewer?) patients in
the USA enroll into clinical trials...**

Very few patients in USA enroll in clinical trials...

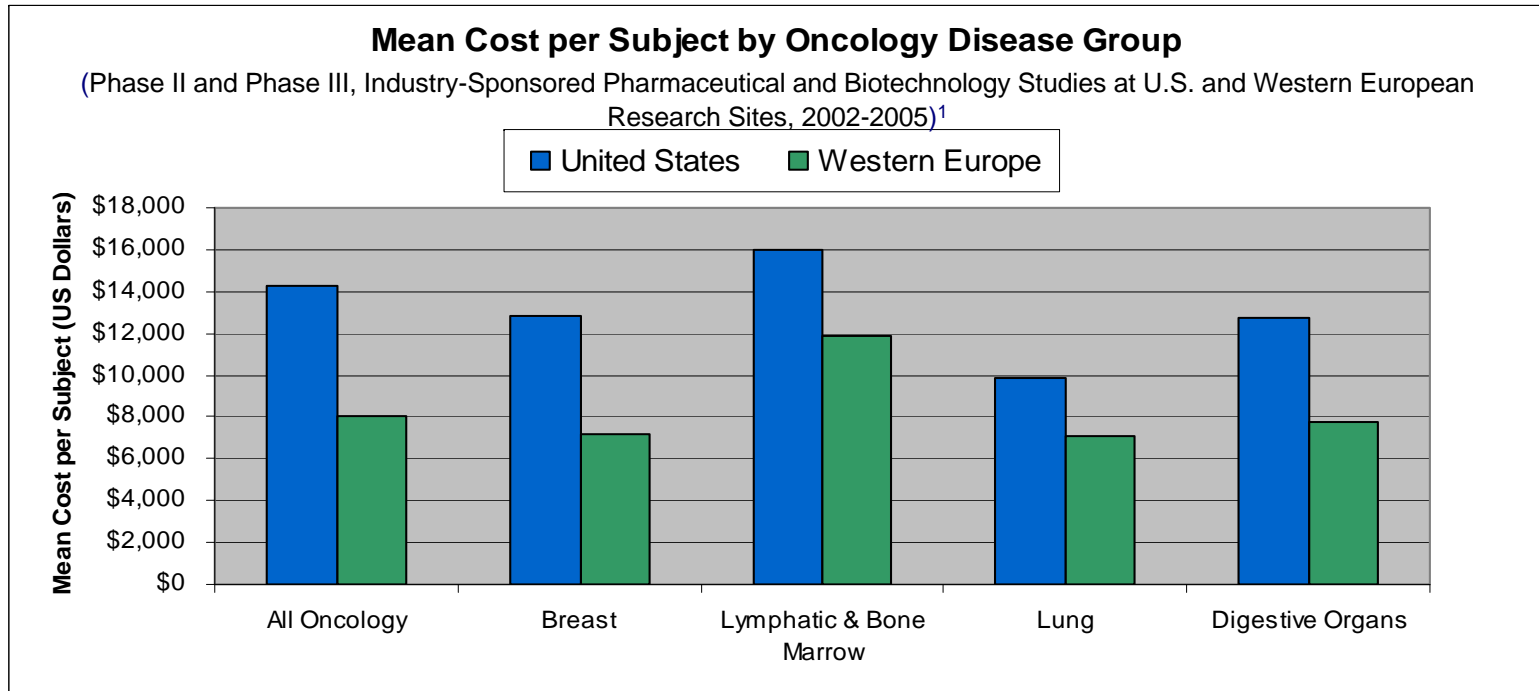
<i>Populations of patients with Metastatic Breast Cancer</i>		<i>Treated Prevalence*</i>	<i>Trial Eligible**</i>
Triple Negative	1 st Line	18,388	919
	Relapsed	19,406	970
Her2+	1 st Line	11,181	559
	Relapsed	9,367	468

*Genentech data on file

**assuming 5% enrollment into clinical trials

Operating outside the USA has Multiple Advantages

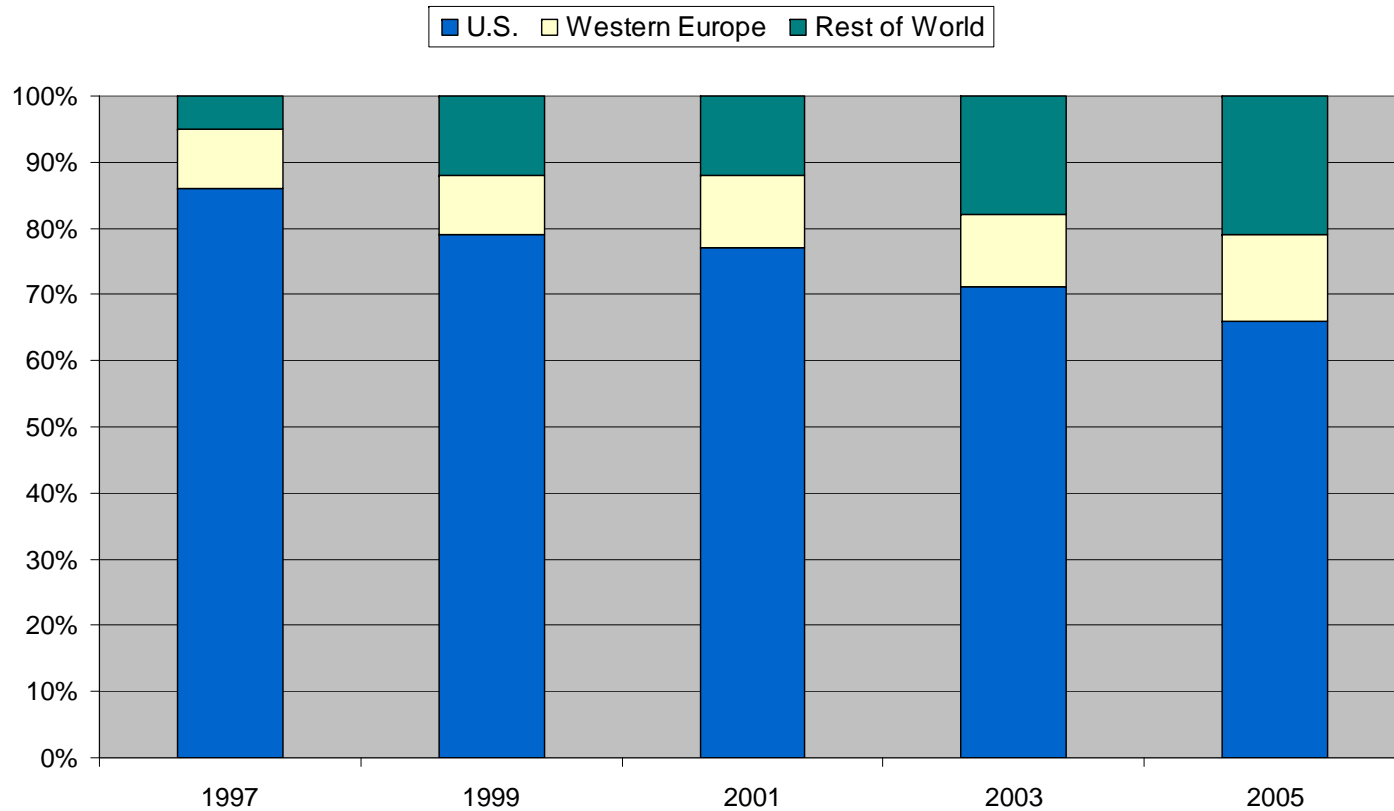
- In the United States, ~3% of patients enroll in oncology clinical trials
- In the United Kingdom, ~17% of patients enroll in oncology clinical trials



1. Source: TrialSpace™ Grants Manager®, the PICAS® database

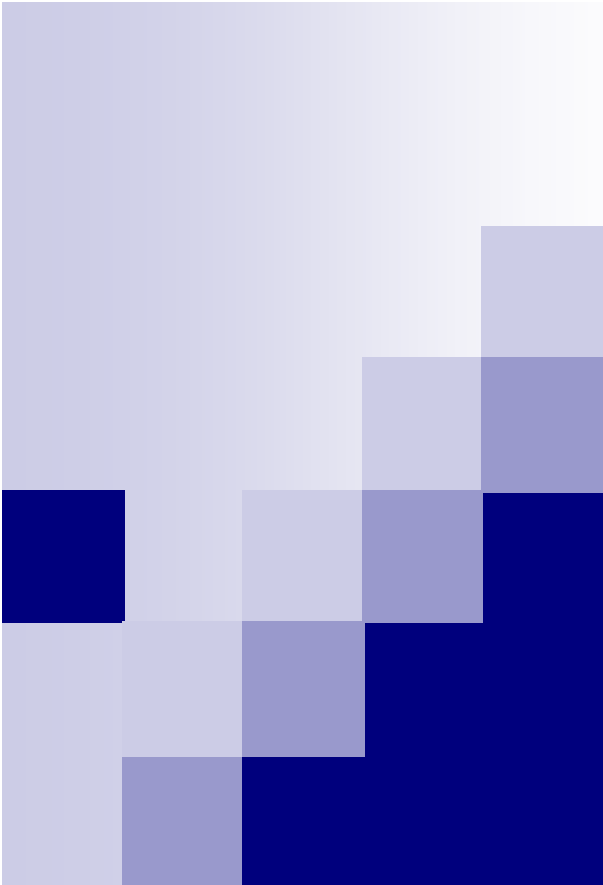
Clinical investigations are going global

Distribution of 1572 Forms by Location of Investigative Site



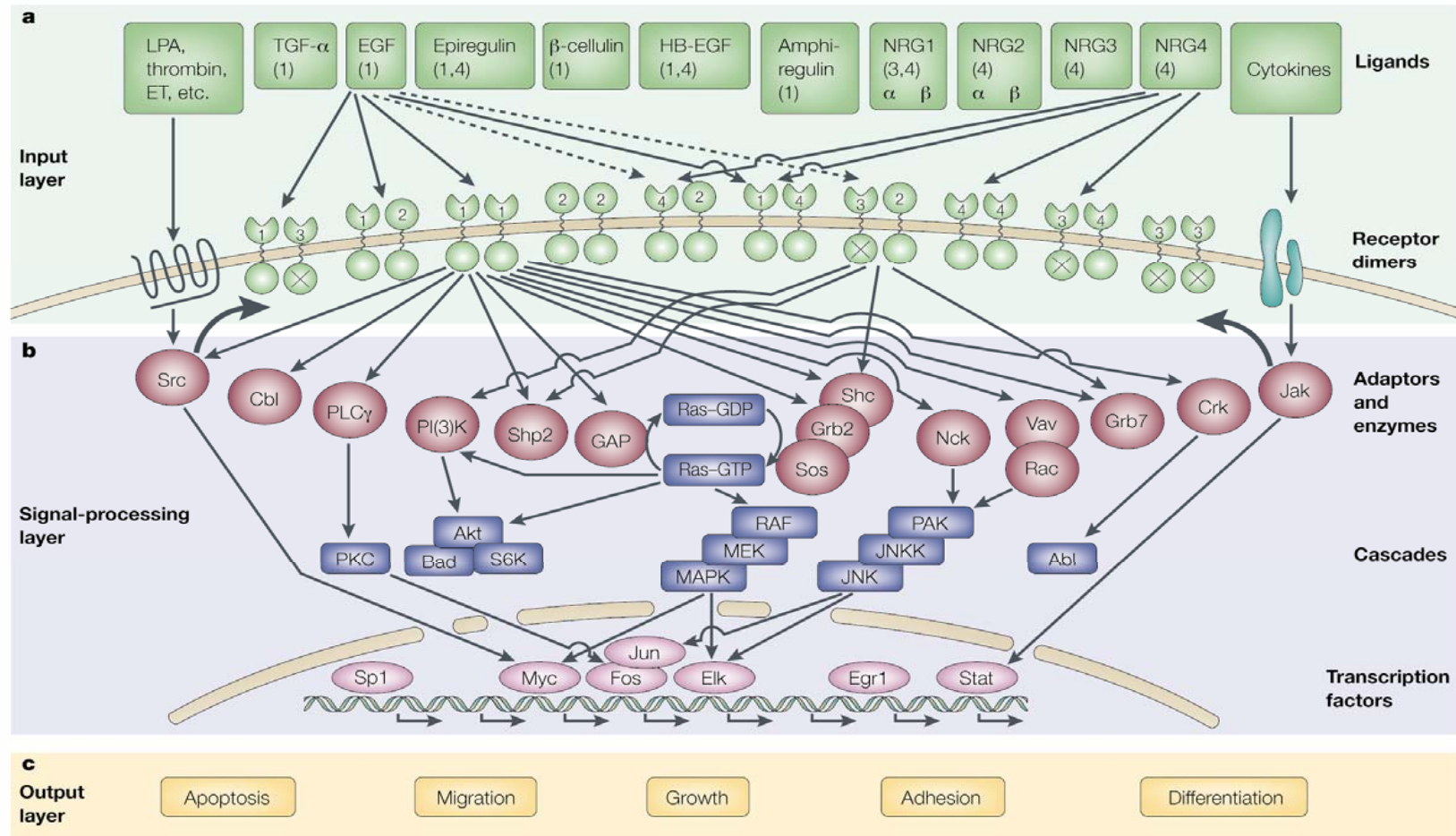
Note: A 1572 form must be submitted to the FDA by a clinical investigator prior to study initiation.

Source: Tufts Center for Study of Drug Development, *Outlook 2007*.



More active drugs leads to longer survival and bigger and more complicated trials...

The HER/ErbB Signaling Network



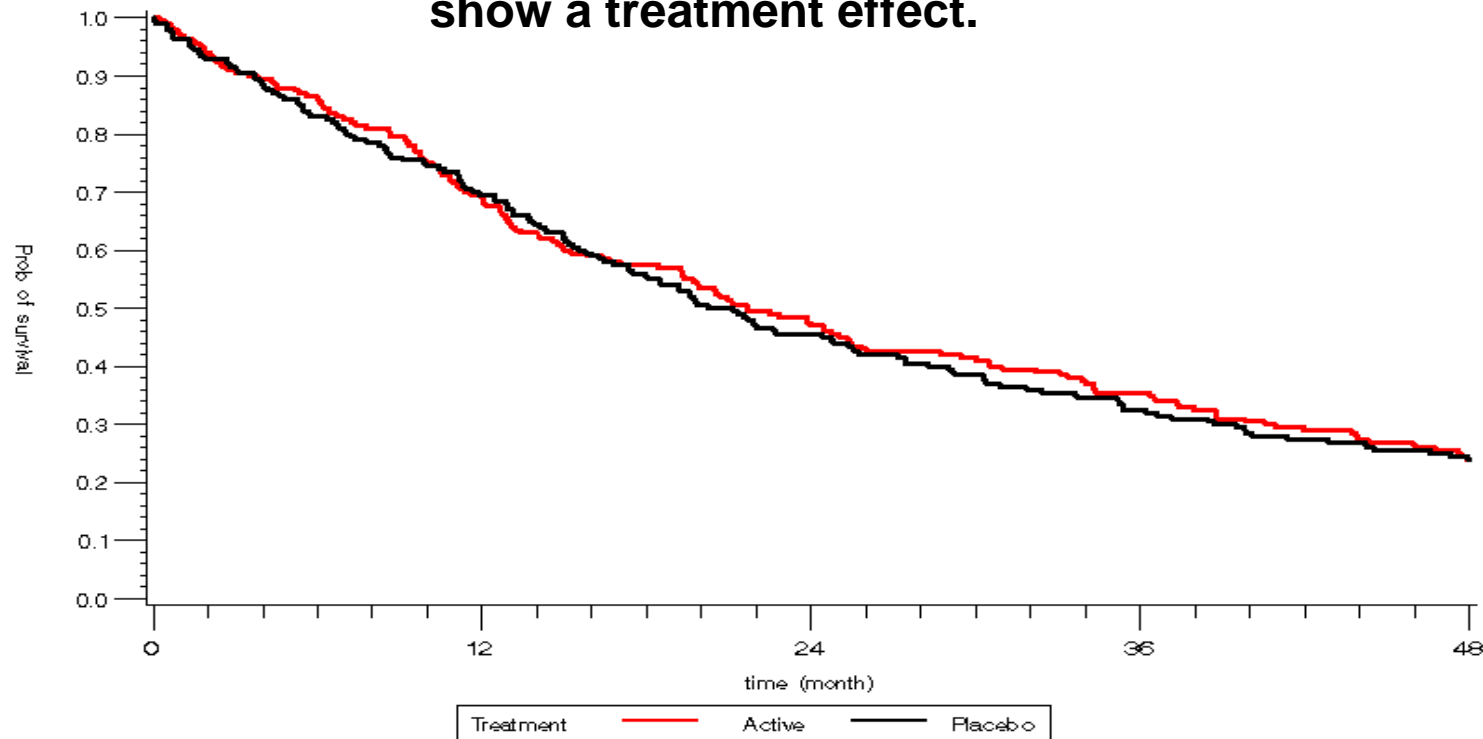
Herceptin® (Recombinant Humanized Monoclonal Antibody to HER2)



- Protects against receptor shedding
- Has no/slight effect on HER2's role as a co-receptor
- Inhibits HER2-mediated signaling pathways
- Applicable *only* to breast cancer tumors that over express HER2

Patient Selection – Without selection, a potentially active new therapy could be missed

A Phase III in which 25% of patients show a treatment effect.

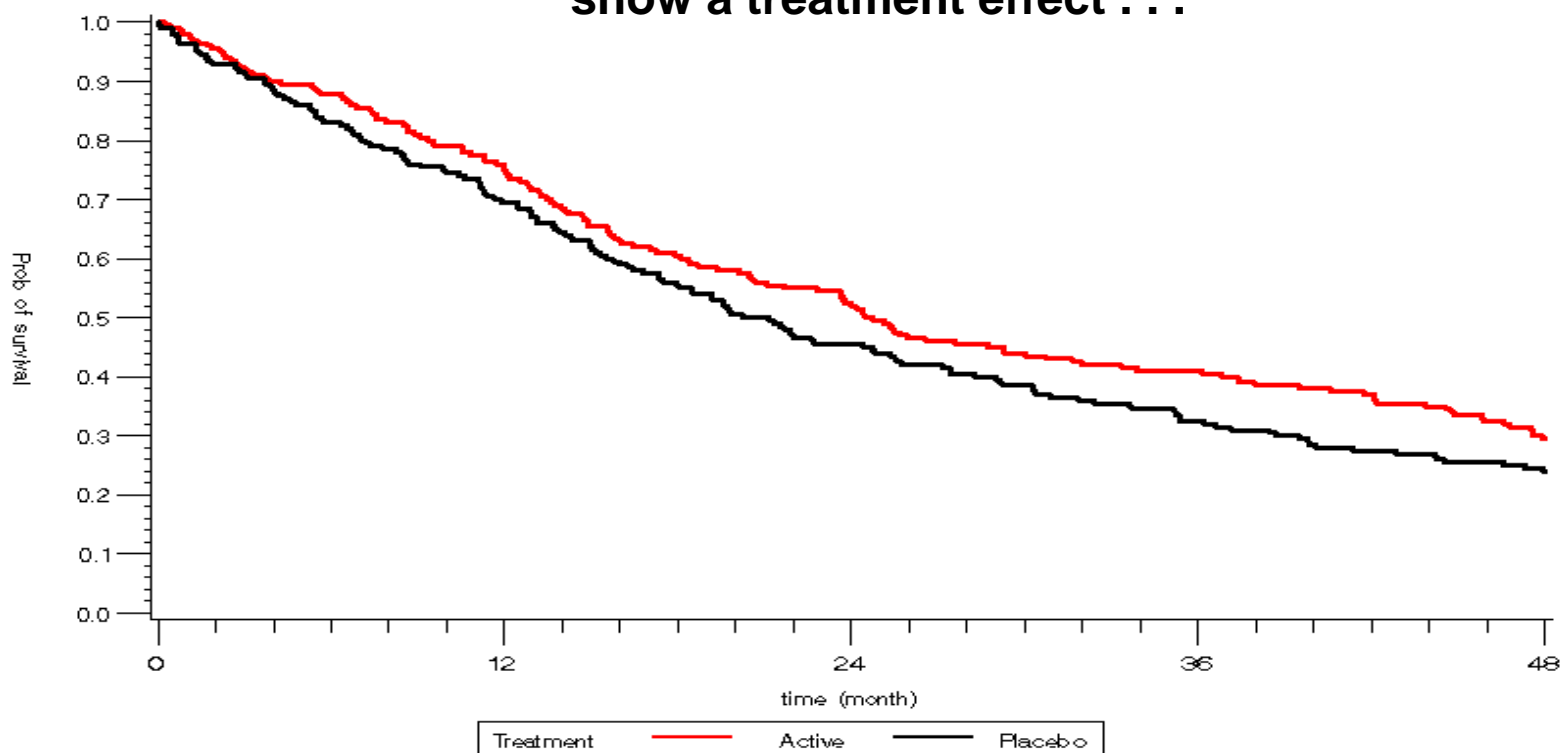


Unverified data and program

Source: Biostatistics(pangcf) pgrn(/immuno/her2/h0648g/current/biostat/kp_simulate)

Patient Selection – Without selection, a potentially active new therapy could be missed

A Phase III in which 100% of patients show a treatment effect . . .



Unverified data and program
Source: Biostatistics(pangcf) pgm(/immuno/her2/h0648g/current/biostat/kp_simulate)

Targeting certain subpopulations of patients creates a barrier to enrollment

Example: First Line MBC (median survival ~ 22 months)

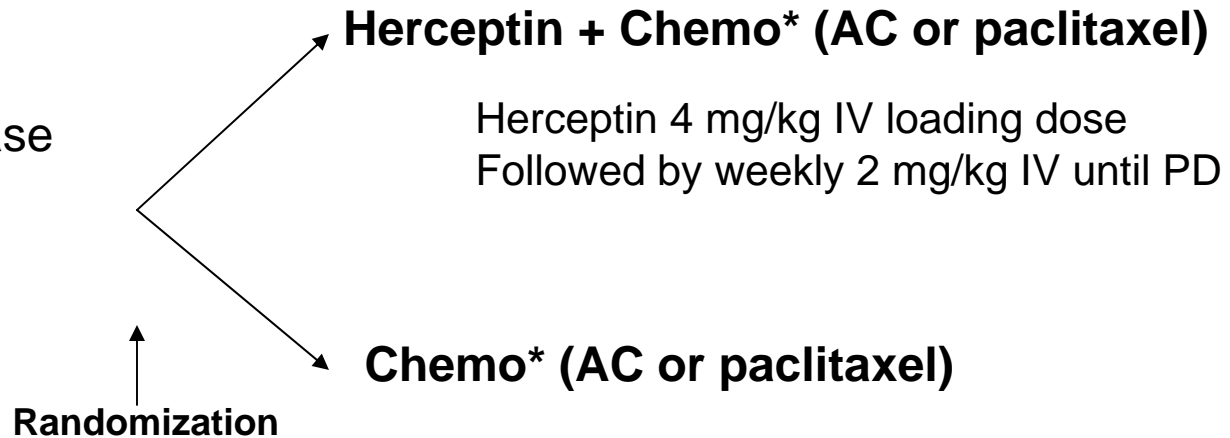
Expected Benefit	Required Sample Size And Study Duration	Target Prevalence	Required "Screened" Population
↑ 5 months (22.7%)	1250 → 52 mos	100%	1250
		50%	2500
		25%	5000

* *Need a specimen, wait for test results.*

* *Need to screen many patients.*

Herceptin® Combination Pivotal Trial: Study Design

- **HER2+ MBC**
- Measurable disease
- No prior cytotoxic chemo for MBC
- $KS \geq 60\%$
- **N=469**

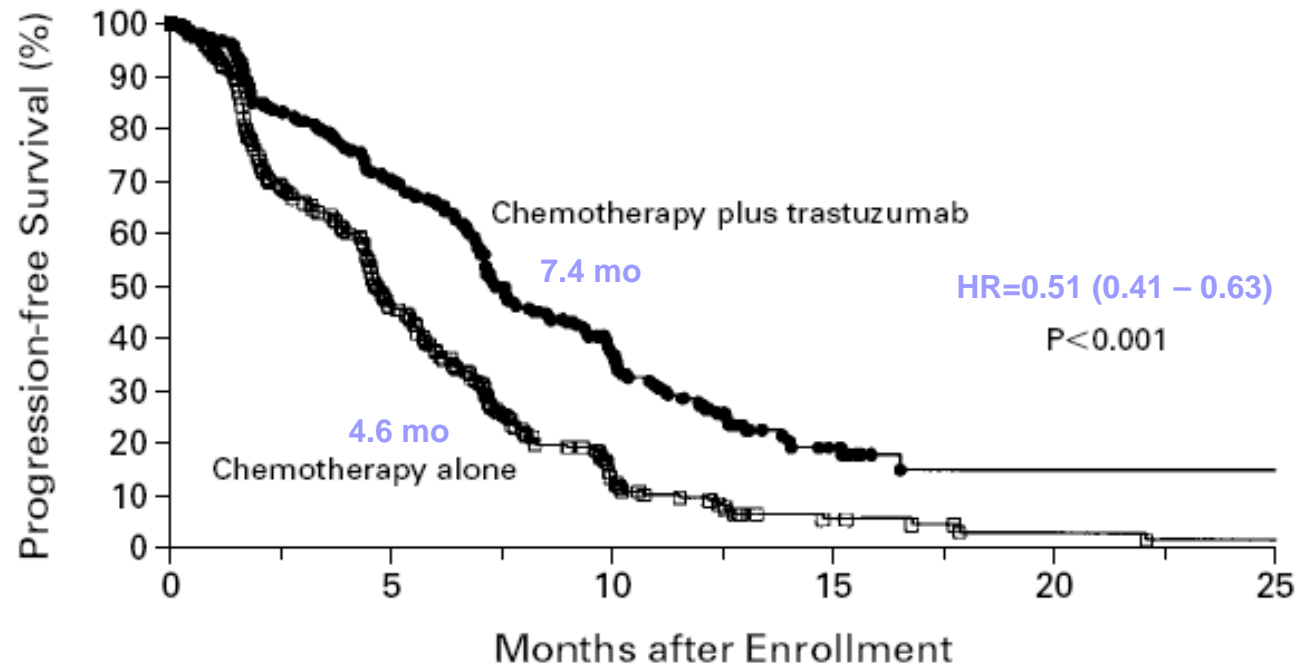


- Primary endpoint: TTP by independent blinded review
- Secondary Endpoints: ORR, DOR, TTF, OS, QOL, PK
- 90% power to detect a 50% increase in TTP (Hazard Ratio=0.667), corresponding to an increase in median TTP from 8 to 12 months
- No formal powering of overall survival in study protocol

Herceptin® Combination Pivotal Trial

First Line MBC: TTP

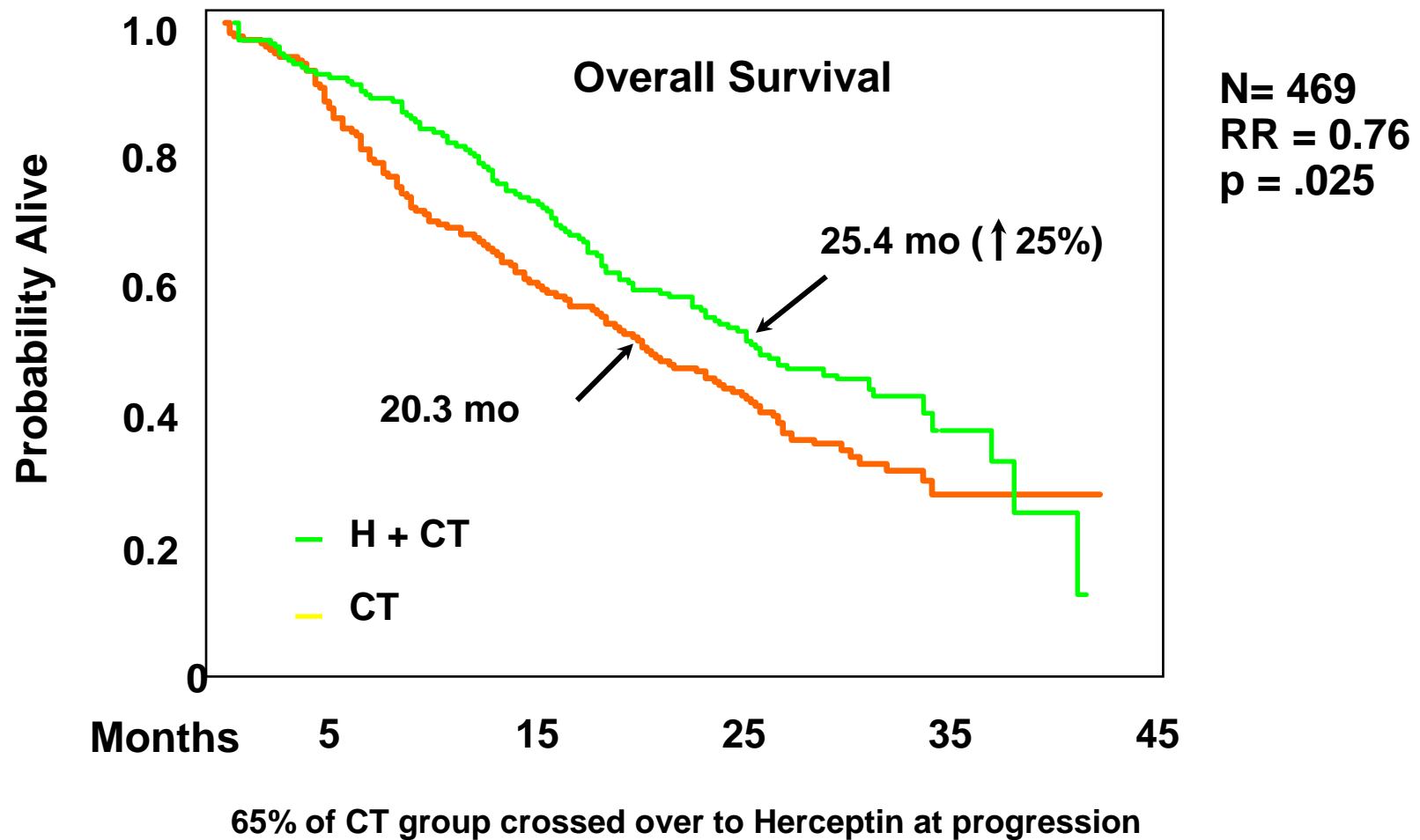
A



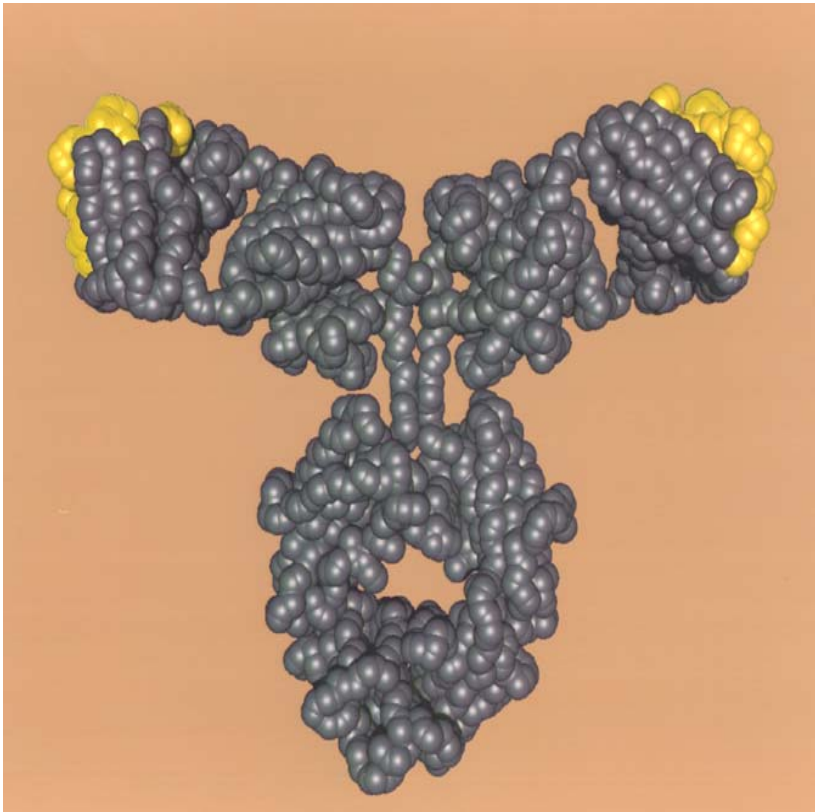
No. AT RISK

Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

Phase III Trial Herceptin® & Chemotherapy First-Line Metastatic Breast Cancer

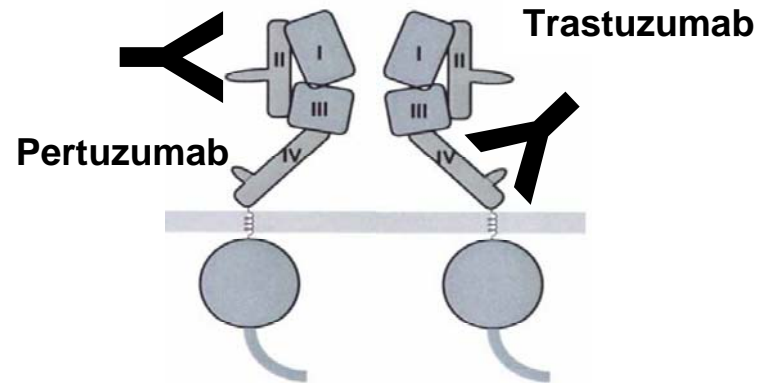


Pertuzumab® (Recombinant Humanized Monoclonal Antibody to HER2)



- Does not prevent receptor shedding
- Has a major effect on HER2's role as a co-receptor
- Inhibits multiple HER-mediated signaling pathways
- Potentially applicable across a wide range of tumor types, both HER2+ amplified and HER2 "normal"
- Adds to activity of Herceptin in HER2+ over-expressing tumors

Multiple Ways to Win with Trastuzumab/Pertuzumab Combination Therapy in HER2 Amplified Breast Cancer

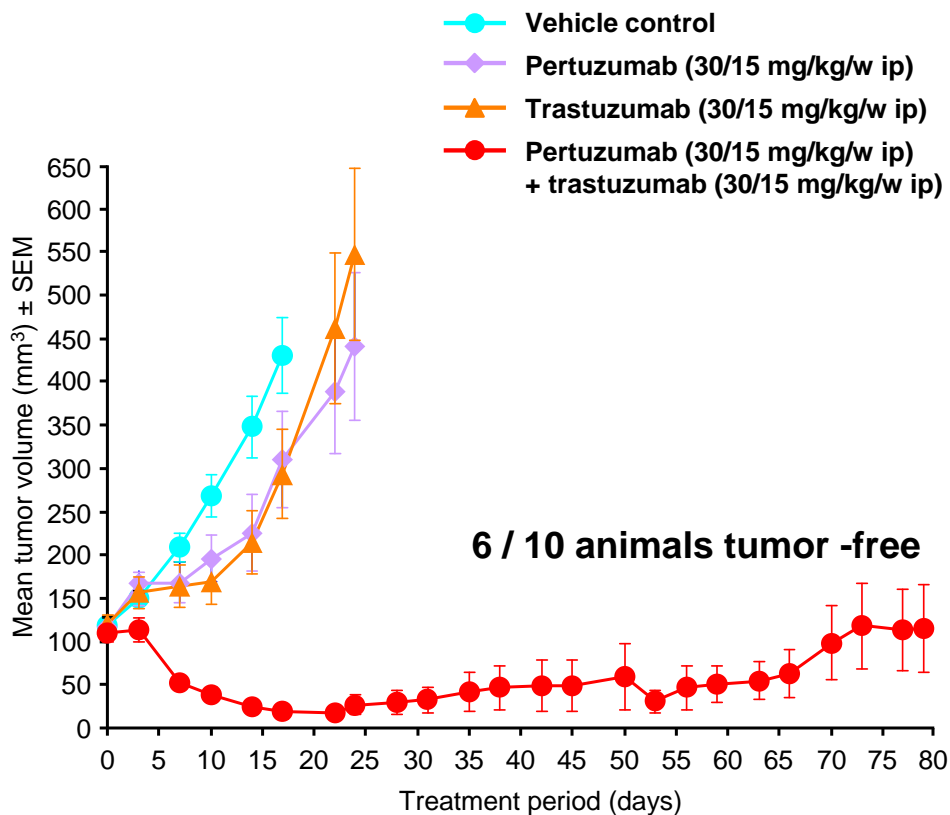


- Blocks HER2's role as a co-receptor in ligand activated complexes
 - Prevents HER2 shedding.
 - Decreases HER3/PI(3)K/AKT signaling.
- Allows for 2 HER2 antibodies to engage a single HER2 receptor.
- Allows for the formation of hyper-cross linked HER2 complexes.
- Twice the number of Fc's per HER2 will allow for more efficient engagement of Fc γ receptors on immune effector cells.
- Takes advantage of the favorable pharmacological properties of monoclonal antibodies.

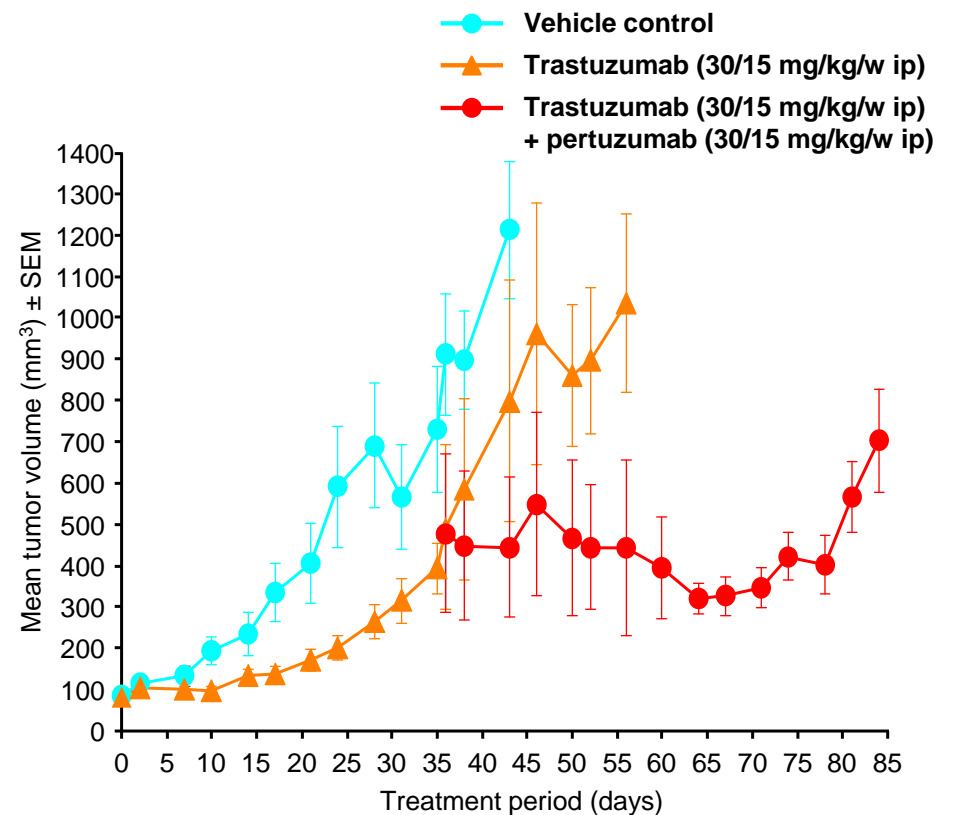
Pertuzumab in HER2-positive breast cancer xenograft model KPL-4

Pertuzumab + trastuzumab initial combination

Pertuzumab treatment after progression under trastuzumab



Friess et al, ESMO 2006



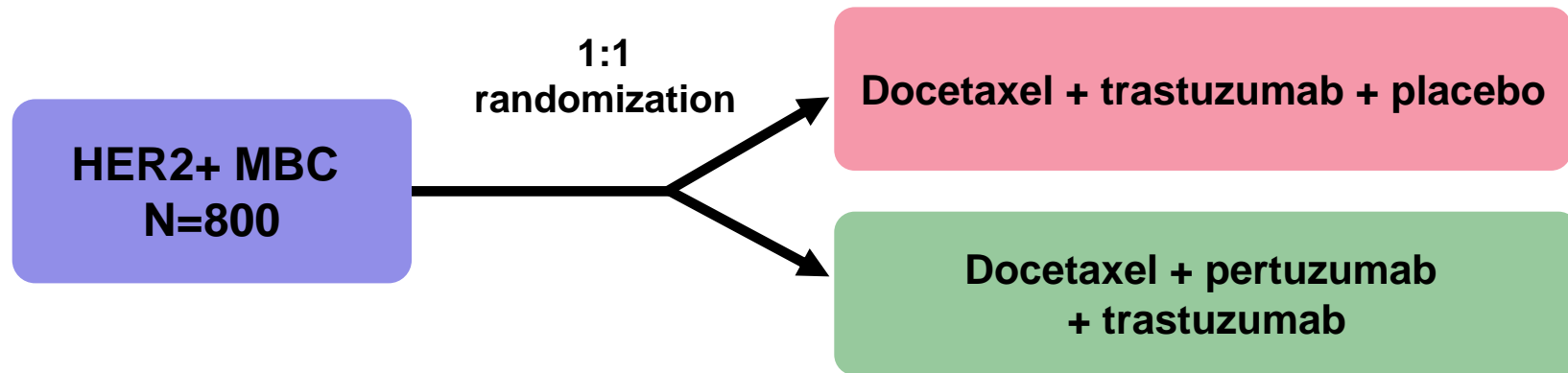
Scheuer, unpublished data

Pertuzumab: HER2+ MBC Studies

Study	Population	Treatment	Efficacy	Key Safety
BO17929 ¹ N=42	HER2+ MBC (prior trastuzumab)	Pertuzumab + trastuzumab q3w	ORR: 18% CBR: 39%	Diarrhea: 57% Non-rash skin toxicity: 35% Nausea/vomiting: 33% Mucositis: 33% Pain: 33%
IST, Swain ² N=11	HER2+ MBC (prior trastuzumab)	Pertuzumab + trastuzumab q3w	PR: 2 patients SD >18 weeks: 3 patients	CHF: 1 patient LVEF decrease: 5 patients Grade 3 infusion reaction: 1 patient

1. Baselga et al. ASCO. 2007.
2. Portera et al. ASCO. 2007.

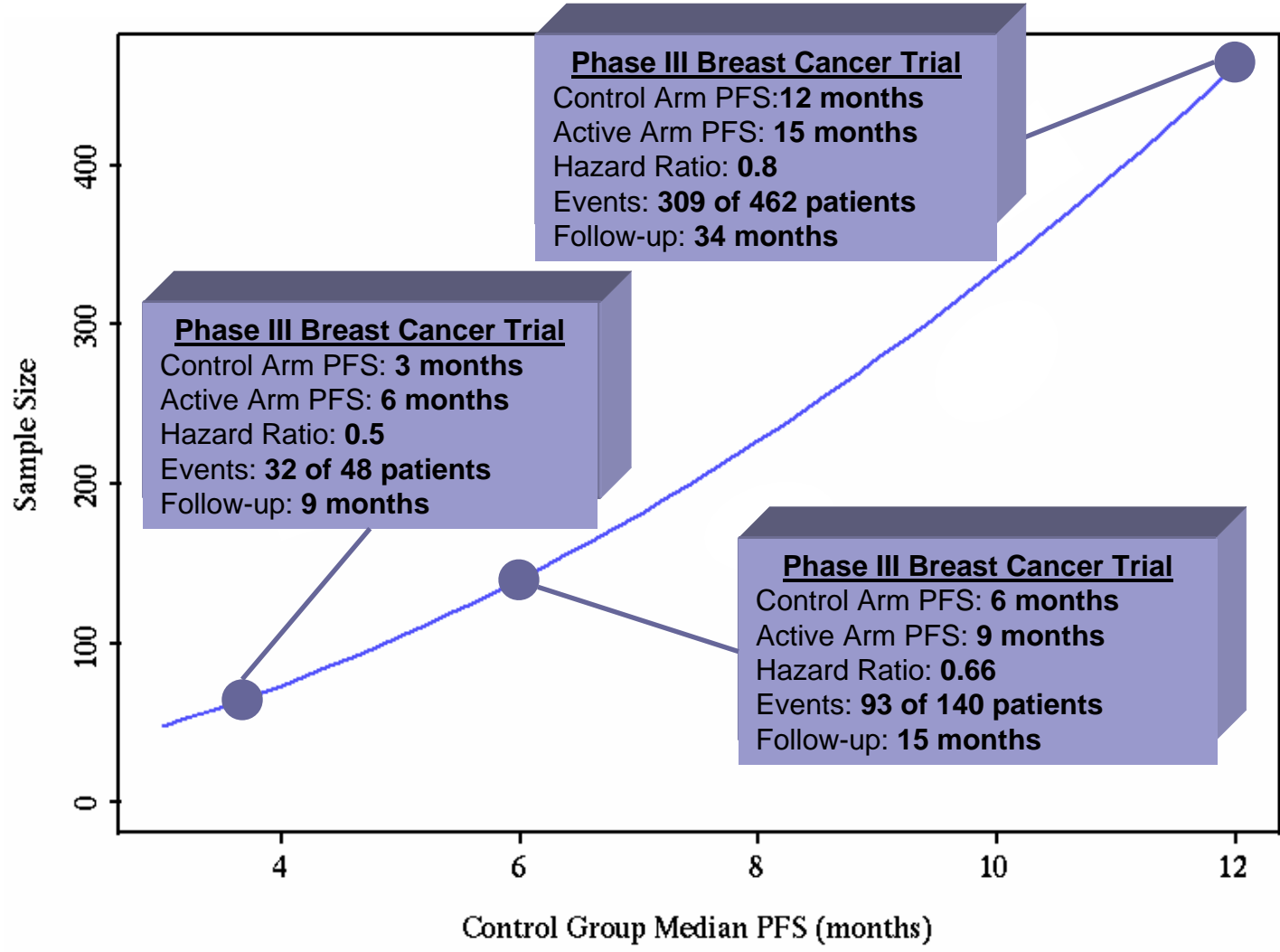
Phase III Study of Pertuzumab/Trastuzumab in HER2+ MBC



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

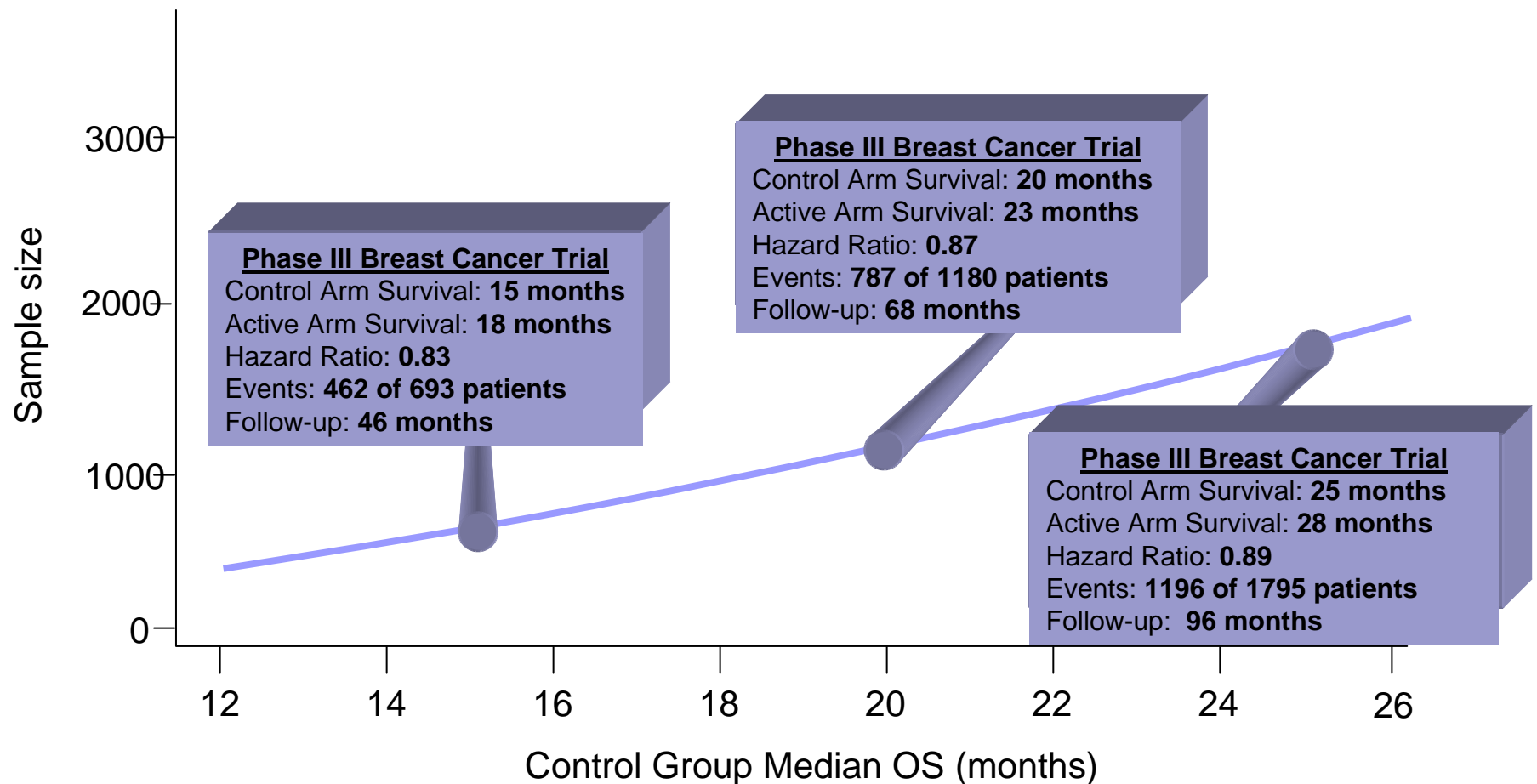
- Enrollment stratified for prior treatment and geographic region of enrollment
- Primary Endpoint: PFS

PFS: A challenging but attainable endpoint in HER2+ breast cancer



Survival: Challenges Posed by an Increasing Control Group Median in HER2+ breast cancer

For a given increase in medians, sample size must increase to reach statistical significance





To understand risk & benefit for patients in the USA health care system, something must change

- **Better drugs**
- **Better understanding of biology so that:**
 - we select patients who will benefit & the benefit is large
 - we co-develop diagnostics and therapeutics
 - we combine the right agents
- **Recruitment of more patients to clinical trials in the USA**
 - Approve drugs for use in the USA based on the risks and benefits established in the medical milieu of the USA
- **Given that smaller populations defined by molecular markers coupled with longer survival may preclude survival endpoints, acceptance of surrogate endpoints such as PFS for full regulatory approval**
- **Novel trial designs evaluating the survival impact of treatment strategies over the course of a disease**



END