

# Personalized Medicine – future impact Pharma industry perspective

**Alison Ayers**

Vice President, Oncology Worldwide Commercial Development,

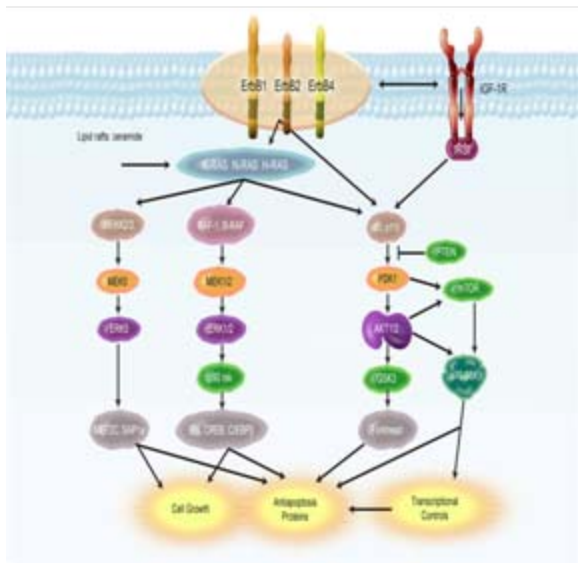
Oncology Business Unit

Pfizer Inc



# What Are We Trying to Accomplish?

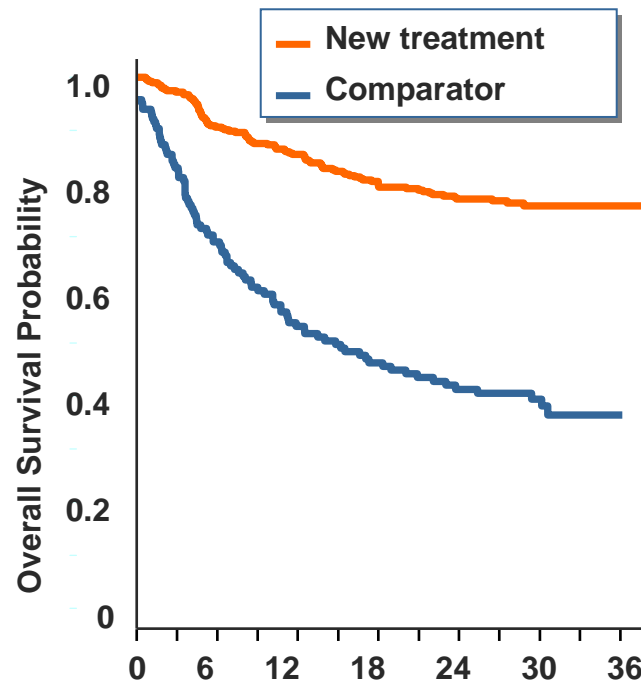
**Right Drug**



**Right Patient**



**Improved Survival**



**Drug targeted to specific oncogene or aberrant pathway driving the specific tumor**

**Patient identified through molecular profiling of their tumor**

**Significant improvement in survival**



# What Are the Issues in “Personalized medicine” Development and Commercialization?

## *Drug Development*

- Identification of the best targets to pursue
- Identification of right biomarker prior to Ph3 initiation
- Complexities of Clinical Trial design for co-development of drug and diagnostic
- Tissue availability

## *Regulatory*

- Path for simultaneous approval of Dx and Tx
- Regulatory pathway for “do-overs” and next generation Dx
- Labeling requirements for companion diagnostics

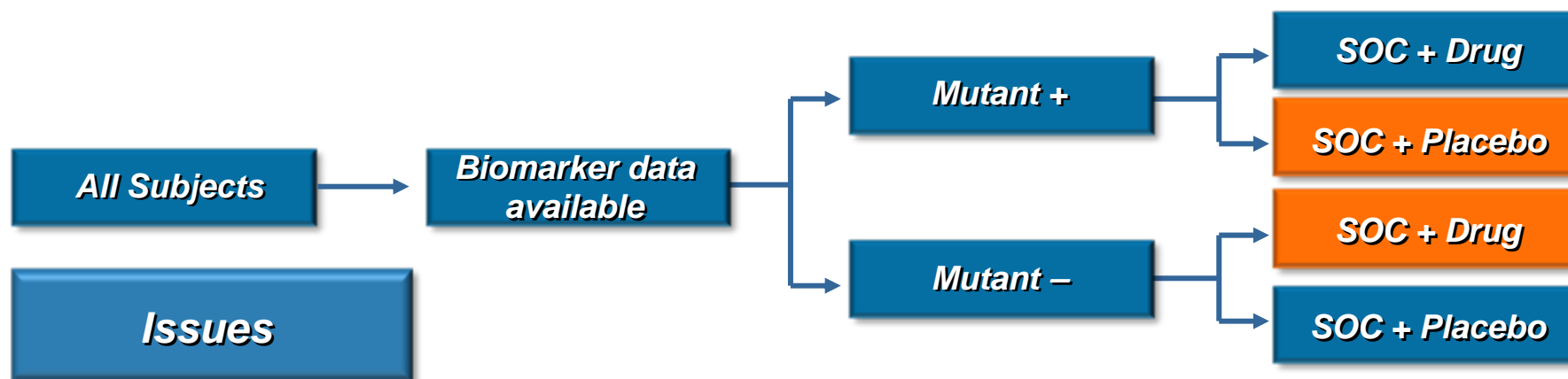
## *Commercial*

- Commercial viability of drug development in small patient populations
- Payer willingness to reimburse
- Cost and access to companion diagnostic
- Logistics



# CDRH View of Optimal Drug/ Diagnostic Co-Development Paradigm

*Clinical test validation of a new diagnostic for use in selecting drug therapy or avoiding drug therapy should be characterized by studying the test in relation to the intended clinical outcome in patient subgroups **with and without the analyte of interest**:*

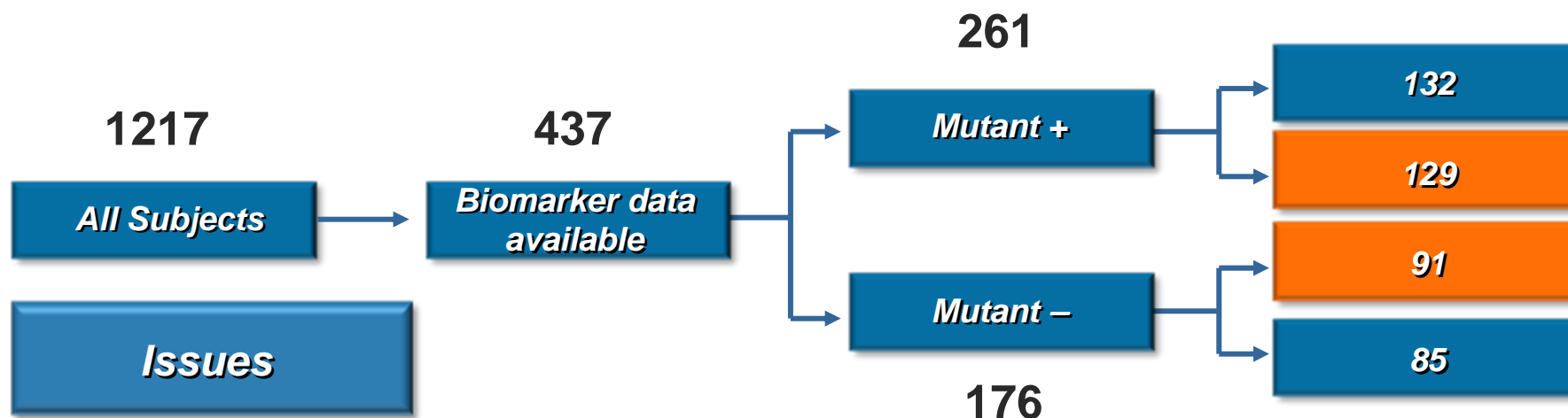


- Complex randomization + extensive molecular profiling means large, expensive, long study
- IRB and patient concern
  - 50% of patients with biomarker WILL NOT get targeted drug
  - 50% of patients WITHOUT biomarker WILL get targeted drug with less likelihood of benefit
- Cross-over resolves some ethical issues, but impairs Overall Survival end-point

# Futur State: Drug and Diagnostic Co-Development Paradigm

*IPASS trial experience: ability to gain molecular data in clinical trial setting*

*Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma; Mok et al, NEJM Sept 09*



**Future State:**

**Streamlined Ph 3 clinical trials focusing on target patient population**  
**Adaptive and cross-over designs; acceptance of PFS as endpoint**  
**Simultaneous approval of companion diagnostic**

# The Challenge of Developing Personalized Medicine for Small Patient Populations

<i>Tumor Type</i>	<i>Molecular Event</i>	<i>Rate</i>	<i>Number of Patients in US</i>
<i>Sarcoma</i>	ALK Translocation	~90%	~75-150 patients
<i>Neuroblastoma</i>	ALK Mutation or Amplification	~20-25%	~200 patients
<i>ALCL</i>	NPM-ALK Translocation	~70-80%	~300-1,200 patients <sup>3</sup>
<i>NSCLC</i>	EM4-ALK Translocation	~3-7%	~7,600 patients
		<b><i>TOTAL</i></b>	<b>~8,800 patients</b>

***Future State: Development and Regulatory Path Based on the Molecular Defect Regardless of Histology***



# Case Study: Gefitinib – First EGFR Inhibitor to Gain (and Lose, and Gain) Regulatory Approval

## May 2003 "All Comers"

- FDA grants accelerated approval in NSCLC on the basis of response rate in 2Ph 2 trials (216 patients)
- Survival data from ongoing Ph3 trials required for full approval

## Dec 2003 No New Patients

- 2 Ph3 trials in unselected patients show no survival benefit
- FDA restricts use of Iressa
  - No new patients
- MAA withdrawn in Europe
- Iressa only marketed in Japan

## Sept 2008 Phenotypic

- IPASS study in selected patients (Asian, never/light smokers) reports positive data
- Iressa superior to standard chemo for Progression Free Survival (HR=0.74)

## April 2009 Genotypic

- EMEA approves Iressa in patients with NSCLC with **activating EGFR mutations**
- August 2009 AZ announces deal with DxS for companion diagnostic for EGFR mutation

## Market Potential US, EU

- ~580,000 patients p.a.

## Market Potential US, EU

- Zero

## Market Potential US, EU

- **130,000**
- never/light smokers with NSCLC

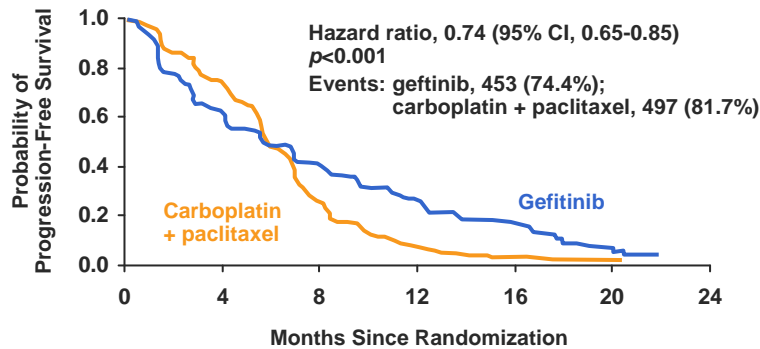
## Market Potential US, EU

- **60-90,000**
- EGFR mutation +ve (assuming US approval can be gained)

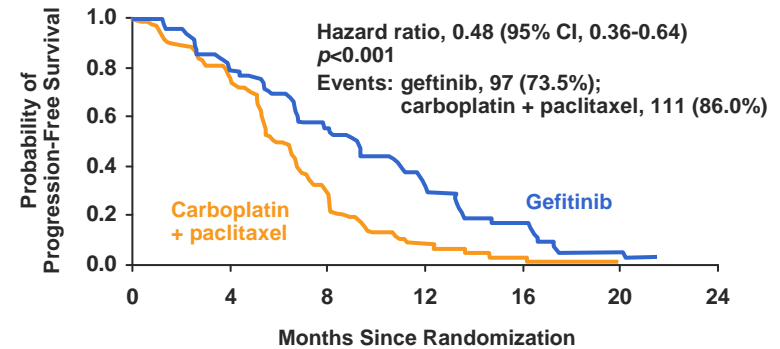


# Gefitinib IPASS study – significant clinical benefit in mutation positive : negative impact in mutation negative

## Overall: Phenotypically Selected Population

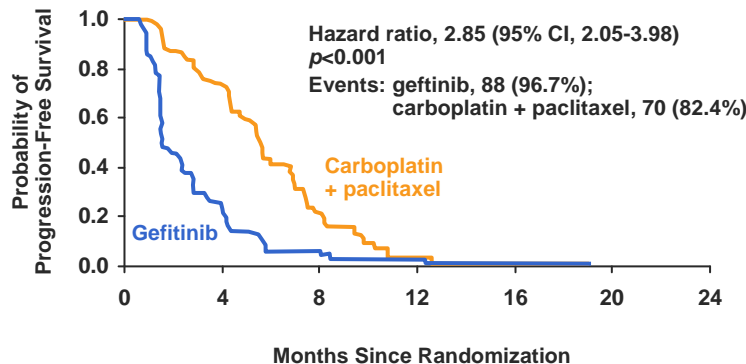


## EGFR-Mutation – Positive



**Gefitinib Superior to Chemo in EGFR Mutant Population**

## EGFR-Mutation – Negative



**Chemo Superior to Gefitinib in Mutation Negative Population**

## Future State:

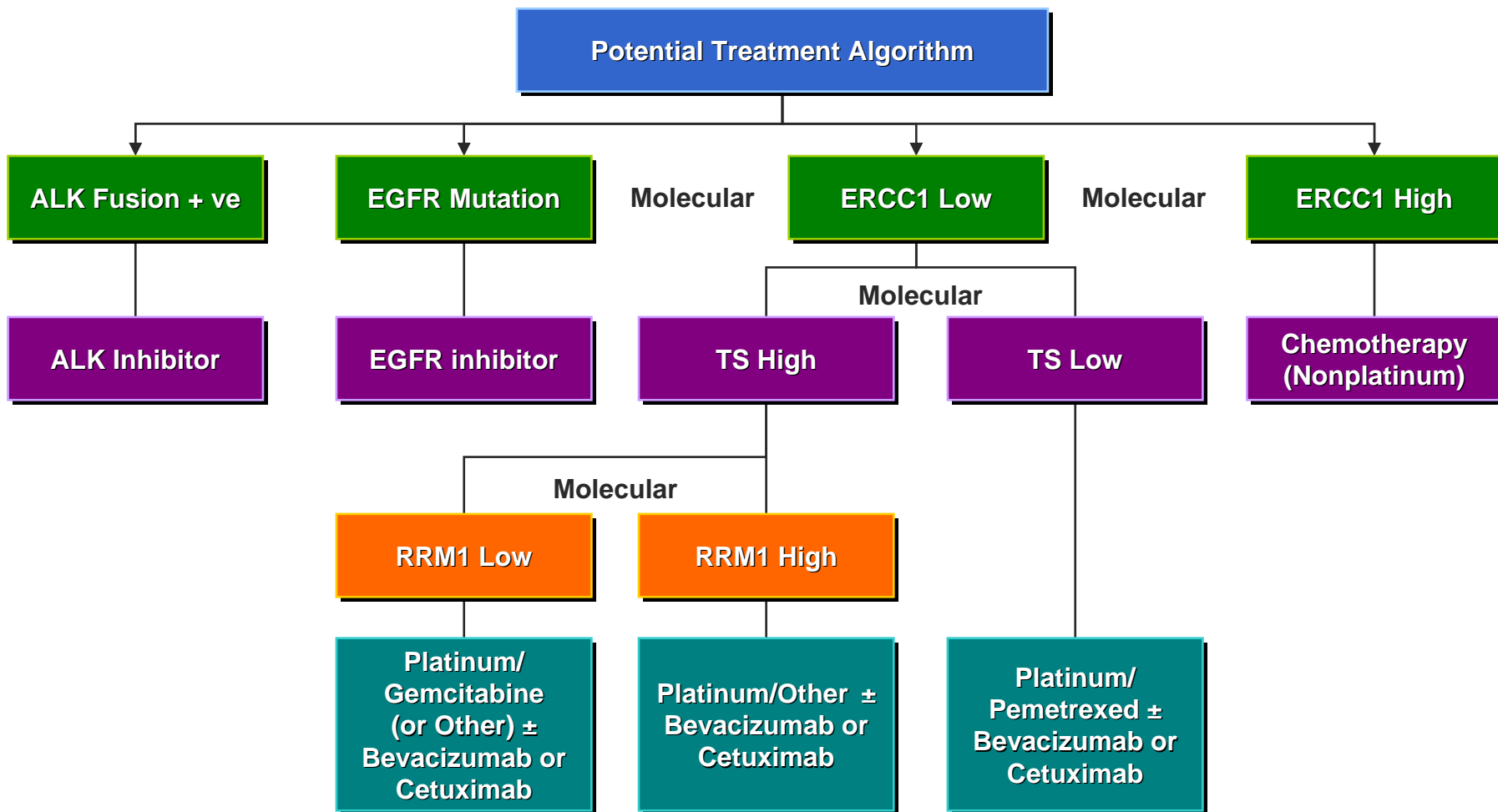
- Knowledge of the “right” biomarker before initiation of Ph 3
- Genomically guided treatment for lung cancer with extended survival



**Pfizer Oncology**

Mok et al. NEJM 361 (10): 947, Figure 1. September 3, 2009

# Potential Treatment Algorithm for Advanced-Stage Non-Small-Cell Lung Cancer: (Good Performance Status): 2012



Adapted from: Gandara DR et al. *Clin Lung Cancer*. 2009;10:6; 392-394.

# The Issue of the Tissue



*Fine Needle Aspirate*

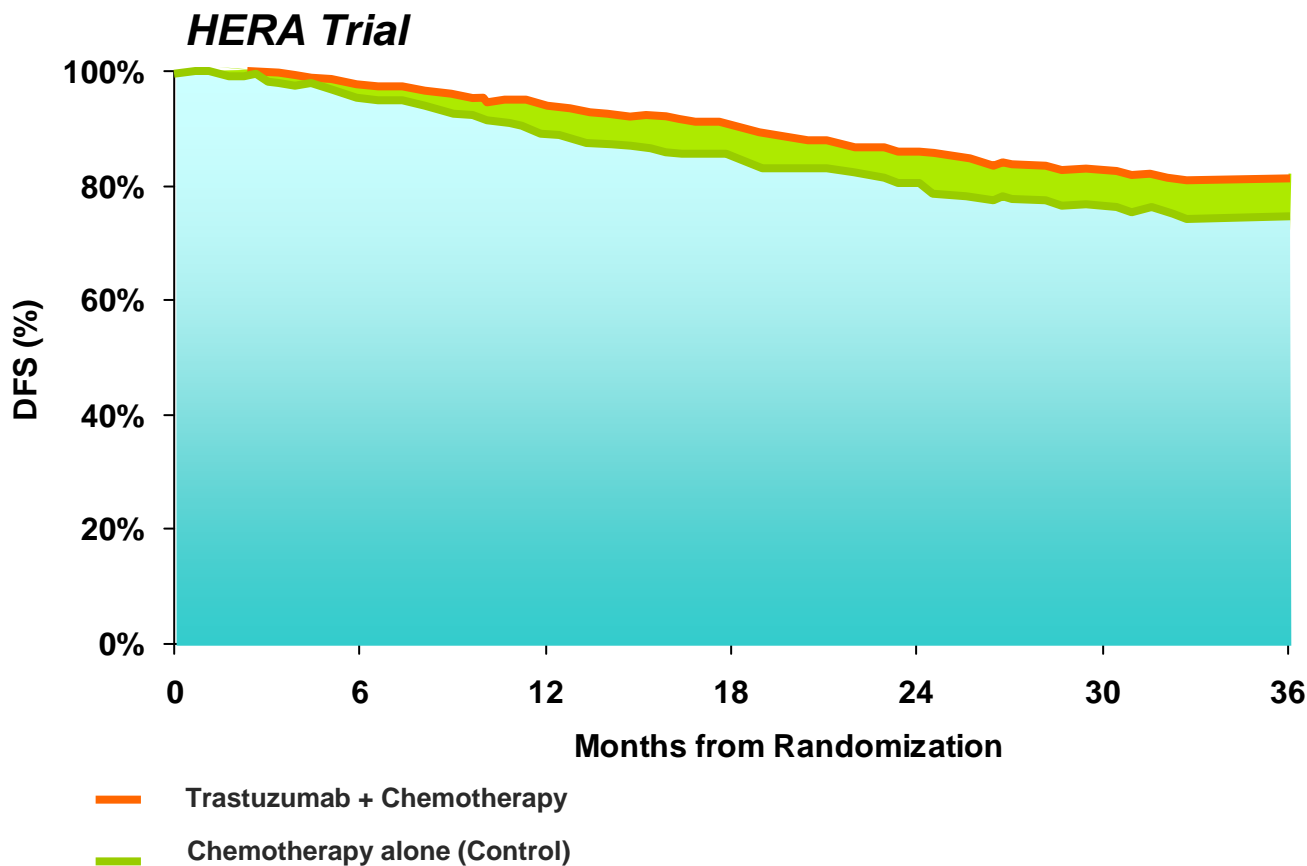
## *Potential Genomic Tests for Lung Cancer Treatment Decisions*

<i>EGFR Amplification</i>	<b>IHC</b>
<i>EGFR Mutation</i>	<b>PCR</b>
<i>EML4-ALK</i>	<b>FISH</b>
<i>ERCC1</i>	<b>IHC</b>
<i>RRM1</i>	<b>IHC</b>

- Limited availability of tissue via fine needle aspirate
- Varying tissue acquisition sources
- Cost of conducting multiple molecular diagnostic tests

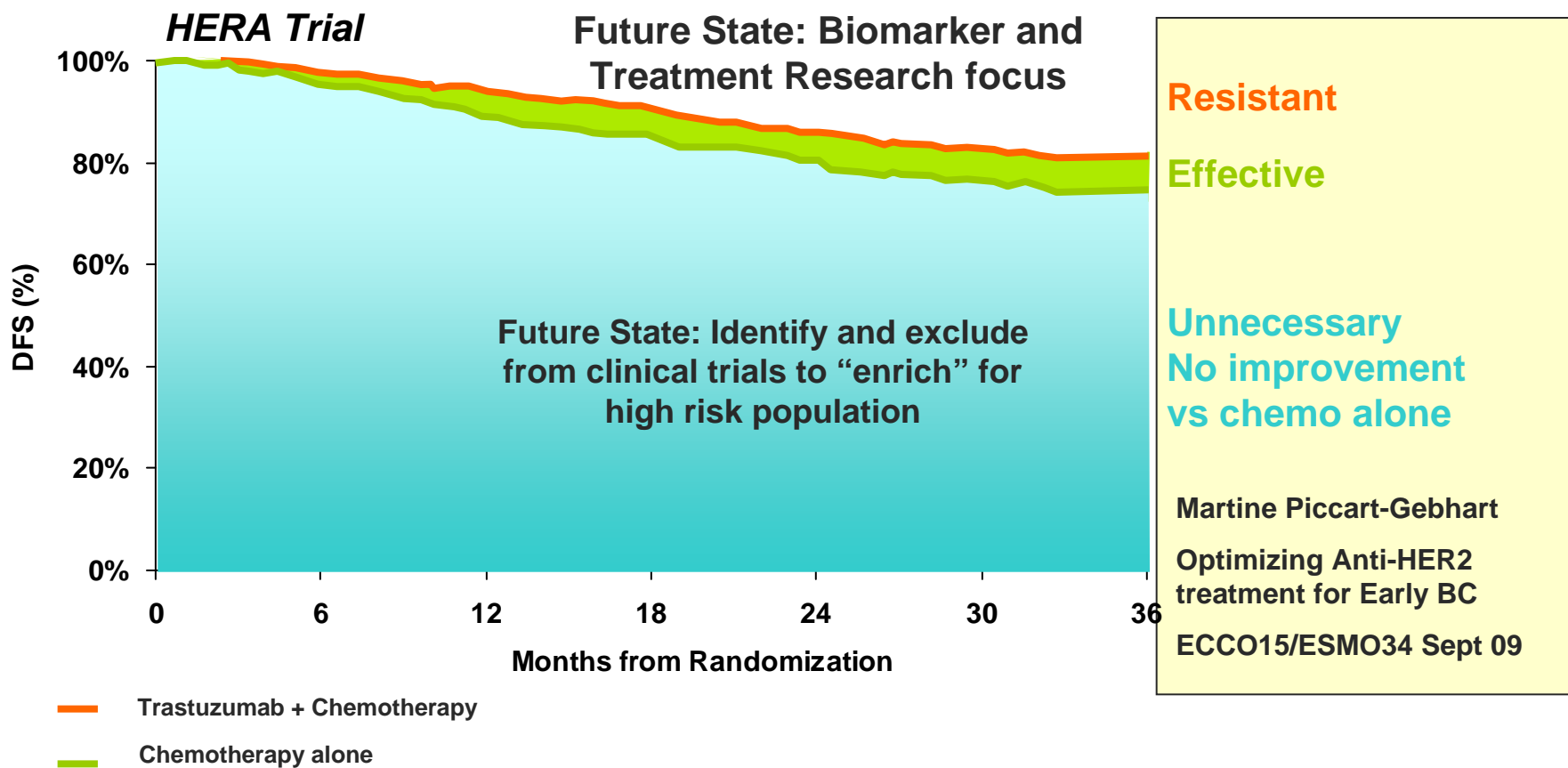
***Future State:***  
***Multi-plex tests to optimize data from limited tissue***  
***Next generation and non-invasive tests***  
***Clear regulatory path for approval***

# Impact of Personalized Medicine on Adjuvant therapy for Breast Cancer : the impact of Her2 Mab



	<i>Events</i>	<i>3-Yr DFS</i>	<i>HR</i>	<i>95% CI</i>	<i>p Value</i>
<i>Trastuzumab</i>	218	80.6	0.63	0.53, 0.75	<0.0001
<i>Control</i>	316	74.0			

# Impact of Personalized Medicine on Adjuvant therapy for Breast Cancer : the impact of Her2 Mab



	<i>Events</i>	<i>3-Yr DFS</i>	<i>HR</i>	<i>95% CI</i>	<i>p Value</i>
<b>Trastuzumab</b>	218	80.6	0.63	0.53, 0.75	<0.0001
<b>Control</b>	316	74.0			

# Personalized Medicine Development: Positive and Negative drivers

PHARMA

## *Pros*

- May improve probability of success for drug discovery and development
- May reduce Ph3 study size and costs if end points achieved more rapidly/more robust difference
- Potential for greater clinical benefit in targeted population

## *Cons*

- Label limited to specific population
- May need to pay for Diagnostic development
- Cost and scope of molecular profiling
- May select wrong biomarker e.g., EGFR vs k-ras
- Many logistical issues e.g., tissue availability, regulatory path

PAYERS

## *Pros*

- More compelling “cost per QALY”
- Enables payer to predict budget impact
- Easier to demonstrate higher value for target populations

## *Cons*

- Cost of Diagnostics
- Ability to change clinical practice based on predictive/prognostic diagnostic test
- Dx may become form of “prior auth”
  - Dependent on accuracy of Dx test

# Future opportunity for accelerated Drug Development timelines?

Vol 448 | 2 August 2007 | doi:10.1038/nature05945

*nature*

## Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer

Manabu Soda<sup>1,2</sup>, Young Lim Choi<sup>1</sup>, Munehiro Enomoto<sup>1,2</sup>, Shuji Takada<sup>1</sup>, Yoshihiro Yamashita<sup>1</sup>, Shunpei Ishikawa<sup>5</sup>, Shin-ichiro Fujiwara<sup>1</sup>, Hideki Watanabe<sup>1</sup>, Kentaro Kurashina<sup>1</sup>, Hisashi Hatanaka<sup>1</sup>, Masashi Bando<sup>2</sup>, Shoji Ohno<sup>2</sup>, Yuichi Ishikawa<sup>6</sup>, Hiroyuki Aburatani<sup>5,7</sup>, Toshiro Niki<sup>3</sup>, Yasunori Sohara<sup>4</sup>, Yukihiro Sugiyama<sup>2</sup> & Hiroyuki Mano<sup>1,7</sup>

September 24, 2009

## Pfizer Launches Phase 3 Clinical Trial With Novel Alk Inhibitor In Non-Small Cell Lung Cancer Patients With Specific Gene Mutation

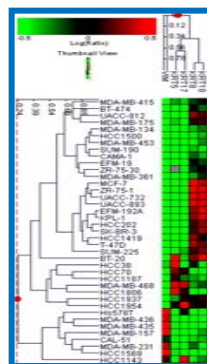
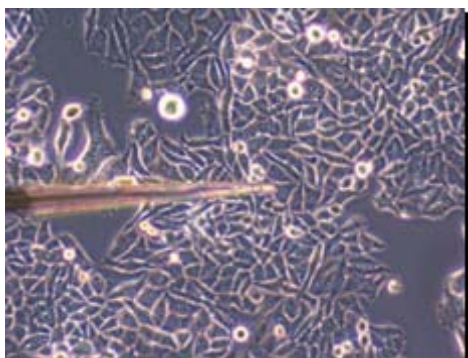


# Future opportunity to reduce ineffective healthcare expenditure

- Simon-Kucher and Partners Spring 2009 *Health Insights Publications*, SK&P reported

*“...in discussions with Simon-Kucher and Partners, most payers have overwhelmingly favored paying for biomarker tests, particularly in oncology. For these payers, the biomarker test is an investment and the goal is to reap the savings of not using the high cost therapies for patients unlikely to respond to treatment”*

# Potential New Drug Discovery and Development Paradigm in the Era of Personalized Medicine



## *Targeted Research*

- Target oncogenes correlated with malignant cell growth and metastasis
- “Roadmap” for development teams for biomarkers and patient selection

## *Molecular Guided Development Plan*

- Molecular guided strategy for clinical trial patient selection
  - Trials in enriched populations to accelerate POC and target higher response/survival
- Focus on poor prognosis patients not well served by current treatments
- Co-development of Companion Diagnostic

## *Right Drug, Right Patient*

- Routine use of Molecular Diagnostics to Guide treatment decisions
- Optimized patient outcomes and improved survival
- Robust Value Proposition