Managing Regulatory Uncertainty: US-FDA Perspectives and Strategies

Workshop on an International Perspective on Pharmacogenetics
OECD
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Outline of Talk

- Genomic Biomarkers
- Strategic Plan for PGx
- Examples of Implementation
- Barriers and Next Steps

Background

Current PGx initiative has been an integral part of FDA operations for 4 years

Catalyst for initiative was industry's hesitance to introduce new innovative technologies

Critical path documented identified *biomarkers* as an opportunity to increase the productivity and success of drug development

www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Sense of Urgency to Enable PGx For Its Benefits

Holds great promise for contributing *biomarkers* to:

1. Target responders
2. Monitor clinical response
3. Identify those at-risk
4. Guide dose selection
5. Differentiate disease diagnosis

Much work needed to be done: qualification of biomarkers for use as tests that are predictive for decisions in drug development, regulatory and in the clinic

Genomic Biomarkers Are Part of a Bigger Picture

Technology is new; intended use is not different than other kinds of biomarkers

- FDG-PET to identify responders ***anatomically***
- PSA to predict at-risk patients ***physiologically***
- HER-2 to differentiate disease ***pathologically***
- Blood levels to guide dosing ***chemically***
- BP to predict disease process ***clinically***

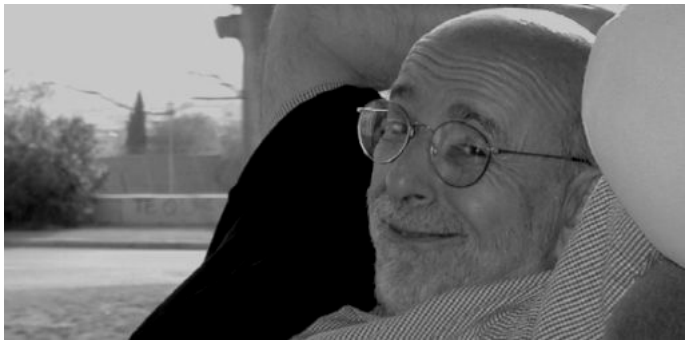
Biomarkers for *Individualization:* Not a Goal of Drug Development Process

Clinical trials look at population effects; they *are not* designed to look at individual differences in response

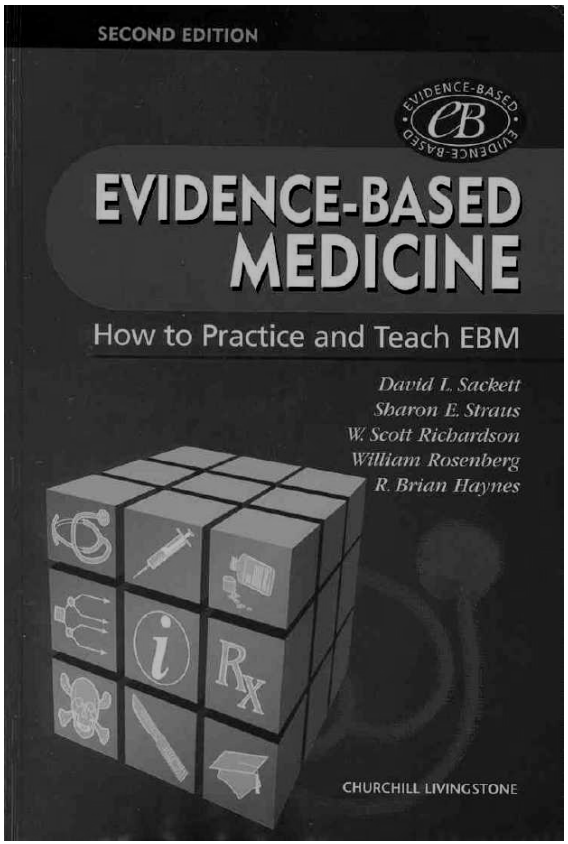
Providers and patients in clinical practice *are not* interested in population effects; they are interested in individual responses

Genomic biomarkers offer a more precise way to distinguish one patient from another in a **prospective way**

Conceptual Framework for Using Biomarkers: Guiding Principles



L.B. Sheiner, Learning vs. Confirming in Clinical Drug Development, Clin Pharmacol Therap 61:275-291 (1967)

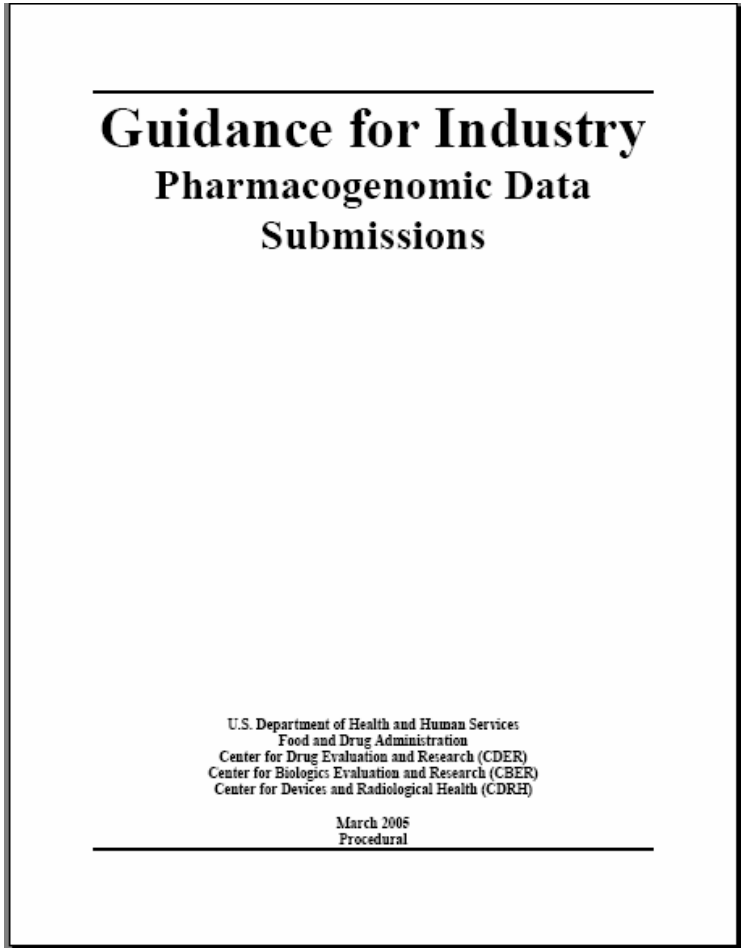


Strategic Plan for PGx: Progress and Reasons for Optimism

Objectives	Goals	Significant Progress
*Convene multiple public stakeholder meetings **	*To get public input and identify critical issues*	*5 workshops and 3 published proceedings*
Create new regulatory pathway and guidances	*To encourage use of PGx and submissions*	*Functional "safe harbor" and IPRG group*
Include PGx in labels of approved drugs	*To facilitate approved clinical diagnostic tests*	*Strattera^{R}, 6MP, irinotecan & warfarin*
Institute a series of educational sessions	*To raise awareness of benefits/limitations*	*Ongoing internal short courses and seminars*
Develop cooperative research agreements	*To provide incentives to speed applications*	*Several partnerships on biomarker qualification*

***** Emphasis on international participation in addition to CIOMS, ICH and OECD*

Development of PGx Guidances



Guidance for Industry

Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

1. Multiplex Tests for Heritable DNA Markers, Mutations and Expression

2. cGMP for Combination Products

3. Drug and Test Co-Development (Draft)

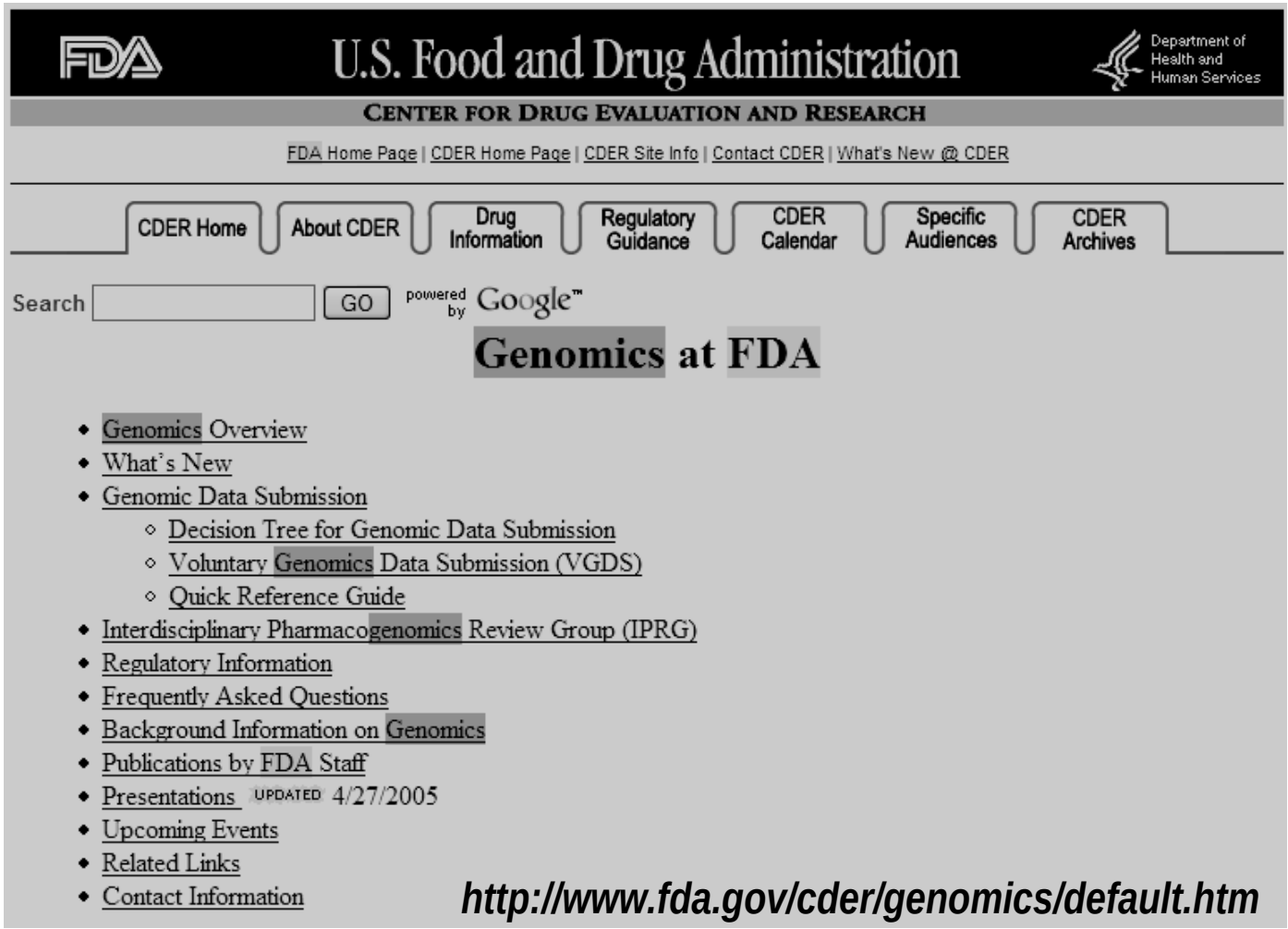
Implementation of the GDS Guidance

- 23 VGDS meeting requests
  - Completed 12 meetings
    - Completed 2 joint EMEA-FDA meetings by videoconference with 2 additional meetings pending
- Alzheimer's, cancer, depression, diabetes, hypertension, obesity and RA
  - Biomarker qualification, biostatistics, clinical utility of microarrays, trial design, database design, software and platforms

Measurement of Value

- Customer surveys after each meeting
- Quality of presentations
- Learning from dialogue
- Repeat business
- Increasing number of companies
- Opportunity to do genomic analysis
- Training of review divisions

Free Information on Internet



U.S. Food and Drug Administration

Department of Health and Human Services

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Genomics at FDA

- Genomics Overview
- What's New
- Genomic Data Submission
  - Decision Tree for Genomic Data Submission
  - Voluntary Genomics Data Submission (VGDS)
  - Quick Reference Guide
- Interdisciplinary Pharmacogenomics Review Group (IPRG)
- Regulatory Information
- Frequently Asked Questions
- Background Information on Genomics
- Publications by FDA Staff
- Presentations UPDATED 4/27/2005
- Upcoming Events
- Related Links
- Contact Information

http://www.fda.gov/cder/genomics/default.htm

Drug Labeling: Legal Basis of Prescribing…..Role of Tests

"If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, *the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug.*"

- 21 CFR 201.57

Survey of PGx in Labels Appearing in PDR (~ 2500 Monographs)

….. 610 drug products have PGx information in label

….. Most information is descriptive only

….. Phenotype most mentioned is AUC

….. No required testing for polymorphic enzymes

..... Black box warning about 2D6 PM for thioridazine

Information deficits in product labels preclude using PGx in clinical practice

Perspective on Product Labels

- **Much of the value inherent in the discovery and development of PGx is lost in uninformative labels**

- **Must put *knowledge (information + skills + experience)* in the value chain of drug prescribing**

> ***"A physician without information cannot take responsibility; a physician who is given information cannot help but take responsibility"***
>
> ***- Paraphrased from Wilbert Leo Gore (Founder of Gore-Tex)***

Labels Must be Updated and Expanded to Use Safely

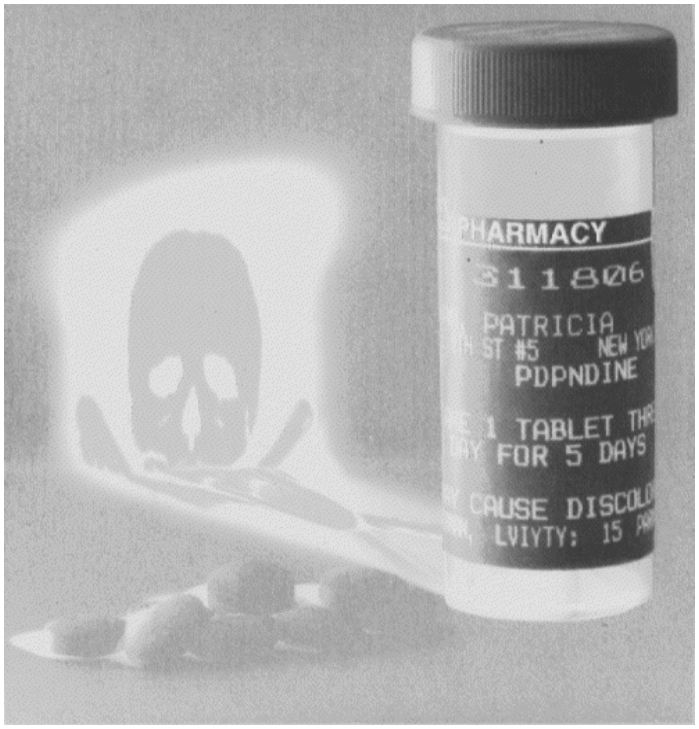
- Jan 2003…..Strattera^{R} (atomoxetine) ~ information on CYP 2D6 in 7 sections of label
- Nov 2003…..Thiopurines (6MP, azathioprine) ~ information on TPMT in label
- Nov 2004…..Camptosar^{R} (irinotecan) ~ information on UGT1A@ in label
- Nov 2005….. Warfarin ~ evidence for CYP 2CP and VKORC1 in label

Principles Related to Relabeling Previously Approved Drugs

- Efficacy is established; safety is provisional
- Risks factors are well-known
  - Epidemiology and post-marketing surveillance
- Extensive patient exposure shows risk differences
  - IMS prescription demographics
- Mechanistic understanding of AEs
- Genetic polymorphisms understood

Main challenge has been to influence or change an existing standard of care….. ”we’ve done it this way for 40 years or we don’t want to risk loss of efficacy”

Shift Thinking From Drug Safety to *Risk Management:* Incremental Value



- No drug is 100% safe
- Concept of *probability* of risk in context of benefit
- *Probability* can change
  - different populations
  - different diseases
  - off-label use
  - duration of treatment

Communicating Magnitude of Risk: *Quantitation*

Event Risk: Grade 4 Neutropenia at 3 Weeks	Adverse Event Rate	Adverse Event Rate	Relative Risk Increase	Absolute Risk Increase	Number Needed to Harm**
	Control Arm	Treatment Arm			
Registration Trial	30%	55%	83%	25%	1/25% = 4

** Only need to treat 4 patients for 3 weeks to cause 1 additional patient to experience Grade 4 neutropenia

Example: Irinotecan ~ Identification of Likely At-Risk Patients

- Irinotecan^{R} (camptosar) ~ proven 2nd line therapy for metastatic colon/rectal cancer
- Providers/patients face a clinical predicament ~ *what is the optimal dose*
  - Incidence of grade 3-4 neutropenia is 35%
  - Nearly 70% of patients need dose reduction
  - Toxicity associated with SN-38 exposure

"…causes severe myelosuppression…"

"...death due to sepsis following myelosuppression…"

"...adjust doses based on neutrophil count…"

Problem with SN-38

- Exposure dependent on metabolism of camptosar by *UGT1A1*
  - Wide interpatient variability in UGT1A1 activity
  - Patients with *28 variant (7 TA repeats) have reduced enzyme activity
  - Homozygous deficient (7/7 genotype) patients have the greatest risk of neutropenia
  - Neutropenia matters to patients
- Original label was silent on UGT information; approved dose not optimized

Risk Assessment by Genotype: Direction of Effect Similar Across Studies

- Would an **adjunct** UGT diagnostic test to identify patients who are 7/7 genotype lead to lower risk of neutropenia vs SOC?

Patient Group	Prevalence	Risk of Neutropenia
All Patients No Test	-----	10 in 100
Wild-type 6/6 Genotype	50%	0 in 100
Heterozygous-deficient 6/7 Genotype	40%	12 in 100
Homozygous-deficient 7/7 Genotype	10%	50 in 100

From Innocenti et al in Clin Pharmacol Ther (2004)

PGx Test of High Quality Not Negotiable: Approval of UGT Test

FDA NEWS

THE FOOD AND DRUG ADMINISTRATION / AN AGENCY OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
P05-53
August 22, 2005

Media Inquiries: **Julie Zawisza**
301-827-6242
Consumer Inquiries: **888-INFO-FDA**

FDA CLEARS GENETIC TEST THAT ADVANCES PERSONALIZED MEDICINE
Test Helps Determine Safety of Drug Therapy

Today, FDA cleared for marketing a new blood test that will help doctors make personalized drug treatment decisions for some patients. The Invader UGT1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. Doctors can use this information to help determine the right drug dosage for individual patients, and minimize harmful drug reactions.

"This test represents the power of DNA-based testing to provide individualized medical care," said Daniel Schultz, MD, Director of FDA's Center for Devices and Radiological Health. "These technologies can significantly improve patient management and reduce the risk of ineffective or even harmful drug therapy by telling doctors how to individualize drug dosing."

Strength of Clinical Evidence: Apply Principles of EBM

- Prospective RCT to show clinical utility of established genomic biomarkers are unlikely for “older drugs”
  - Ideal with least # of biases
  - Far from perfect
    - number of patients, time to complete, multi-center
    - Very expensive ~ who will support them
    - Attrition and compliance ~ compromise data
    - Ethical issues ~ prior information on risk
  - For “older” approved drugs ~ **have priors**
    - Risks well-known; at-risk patients identified
    - Mechanistic hypothesis of AE
    - Cause-effect associations (dose-response)

Other Sources of Evidence

- Case reports, case series or cross-sectional studies
  - Descriptive studies, sometimes without controls
  - Weakest evidence, by itself, they are not compelling
- Case-control studies
  - Use collected data, patients have events, retrospective, presence/absence of outcomes
  - Fair source of evidence, improve if quality of data is good
  - Estimate odds ratio
- Cohort studies
  - Type of observational trial
  - Prospective/retrospective, patients grouped by risk factors
  - Easy to estimate probability of event

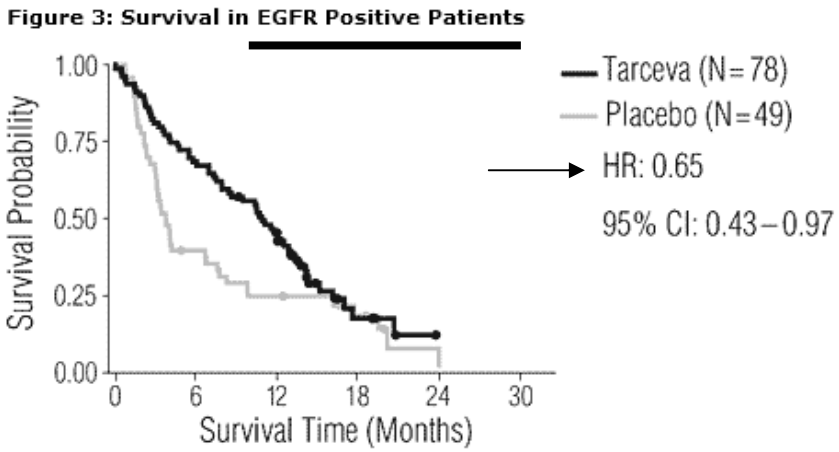
Example: PGx in Label At Time of Approval and Subset Analysis of RCT

- Tarceva^{R} (erlotinib) ~ proven 2nd line monotherapy for NSCLC based on clear survival effect, primary endpoint (n = 731)
- Designed to target EGF receptor of tumor

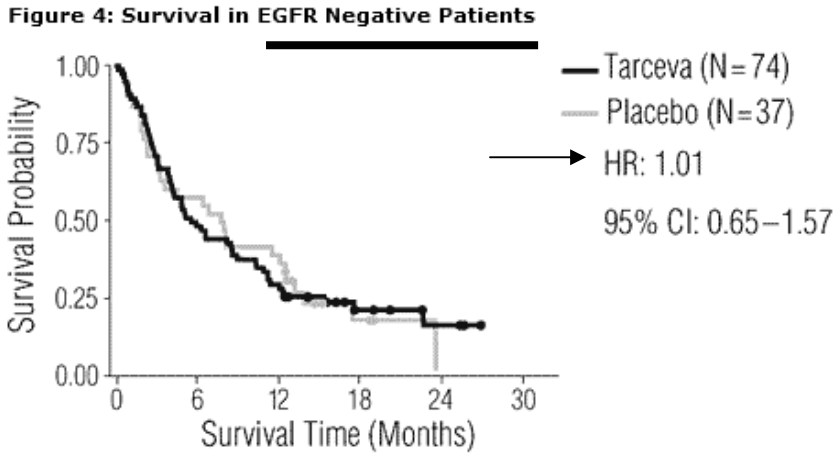
All Patients	Tarceva (488)	Placebo (243)
Median Survival	6.7 mo	4.7 mo
Survival at 1 yr	31.2%	21.5%
Median PFS	9.9 wk	7.9 wk

Differences in Response Due to Tumor Genomics: Subset Analysis of Clinical Trial Patients (n = 238)

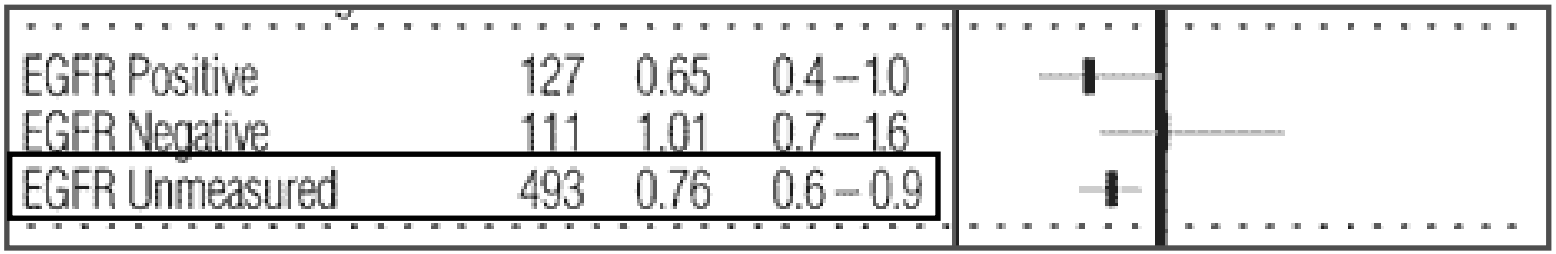
Tumor Response = 12%



Tumor Response = 3%



Hazard Ratios for Death (Drug/Placebo), CI and Forest Plots



Subset Analysis: Strong Prior Assumption That EGFR Status Is Important

- Fully informative but did not recommend EGFR testing (IHC)…..opportunities coming
- EGFR test not required…..caution
  - CI for tumor response and survival overlapped
  - Efficacy in EGFR(-) cannot be excluded
  - EFGR status unknown in 67% of patients
  - Patients not randomized based on EGFR status
  - Only 15% in EGFR (-) subgroup
  - EGFR diagnostic assay not validated
- Two post-marketing studies planned with EGFR pretreatment information

Summary: PGx Is a Work in Progress

- VGDS, label revisions and genomic subset analysis lay groundwork for **future** expectations of biomarkers and reduce **present** uncertainties about disease and drug response
- Regulatory agencies (FDA) can do more
  - Support global harmonization in policies
  - Explore incentive system for using genomics
  - Research on reduction in post-marketing risks
  - Clear expectations for genomics for industry
  - Explore continuous improvement in B/R

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