

Personalized medicine comes to “NSCLC”: 2011

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Clinical Trials in Advanced NSCLC: 2010

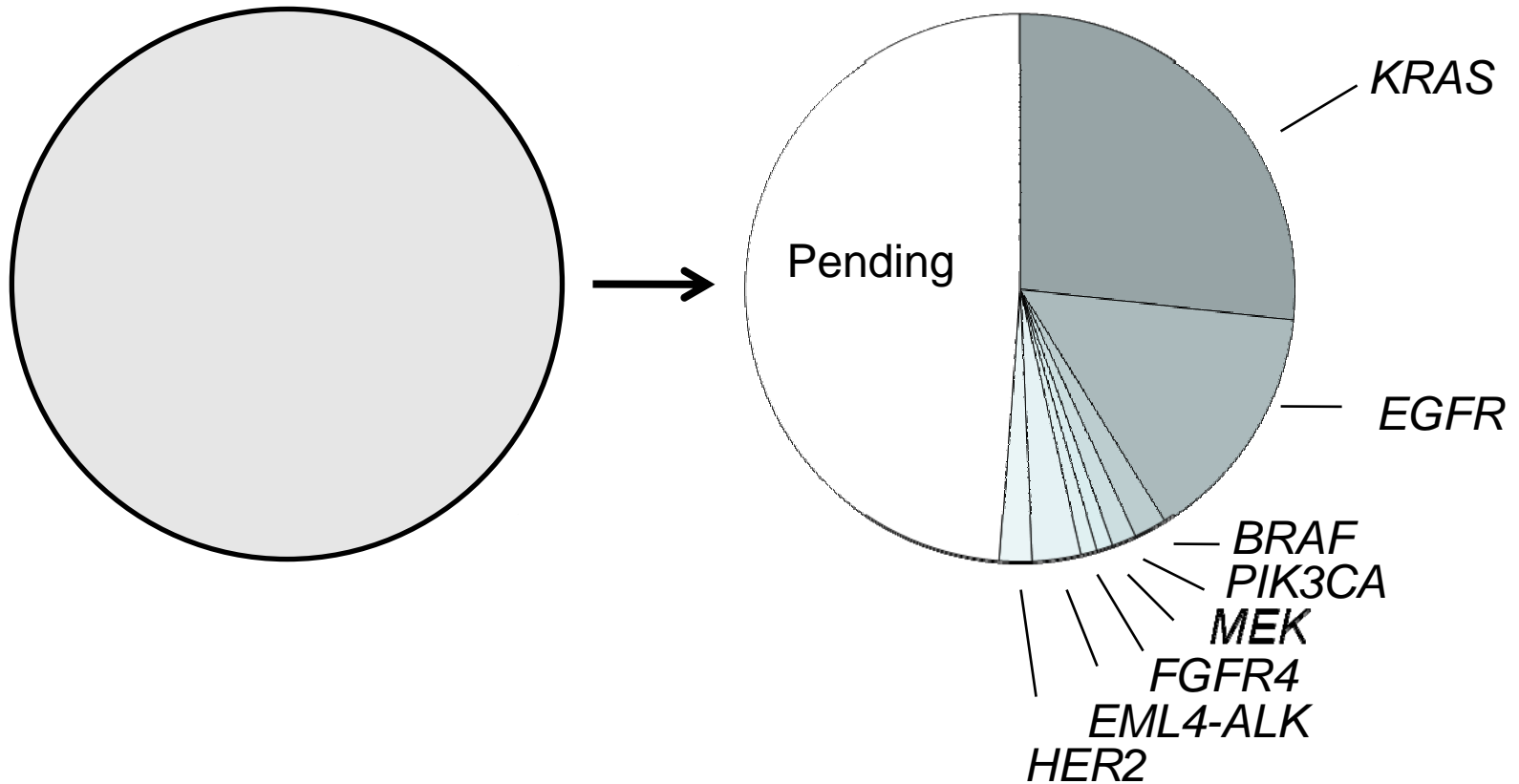
- **Fundamental change in strategy for drug development**
- **“Pre-EGFR mutation”**
 - **Cytotoxic agents and targeted therapies given to unselected pts w “NSCLC”**
 - **Driven by empiricism; developed in 1st /2nd/3rd lines**
 - **KPS, weight loss, gender, bone mets important**
- **“Post-EGFR mutation”**
 - **Distinguishing squamous from non-squamous NSCLC essential**
 - **Molecular determinants of eligibility**
 - **Look across tumor types and lines of therapy for applicability**
 - **Clinical characteristics (phenotype) such as ethnicity, smoking history, and histology provide clues as to genotype**

NSCLC Chemotherapy 1975-2011

	RR	1 yr OS	2 yr OS
No chemotherapy	0%	10	0%
Single agent	15%	20%	10%
Two drugs	25%	35%	20%
Three drugs	35%	35%	20%
Two drugs + bevacizumab	35%	50%	22%

Molecular Subtypes of NSCLC

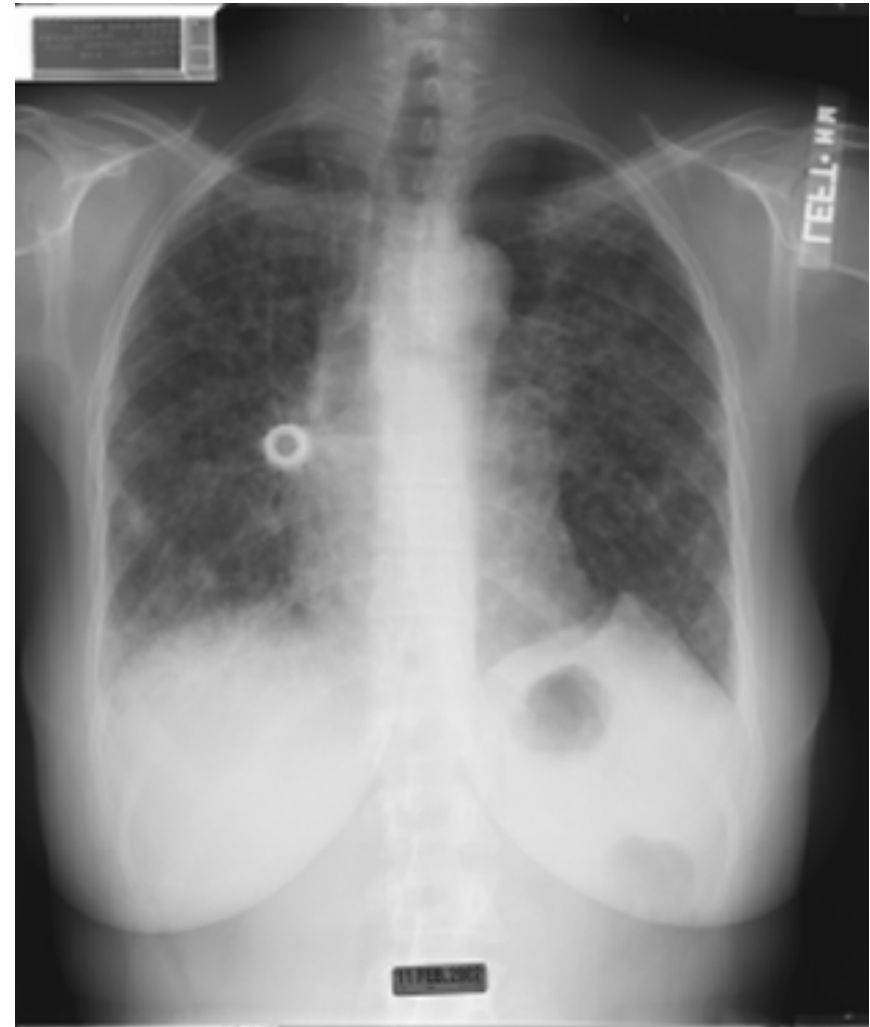
Adenocarcinoma



Why Are 1 in 10 Like This?



6 FEB 2002



11 FEB 2002

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

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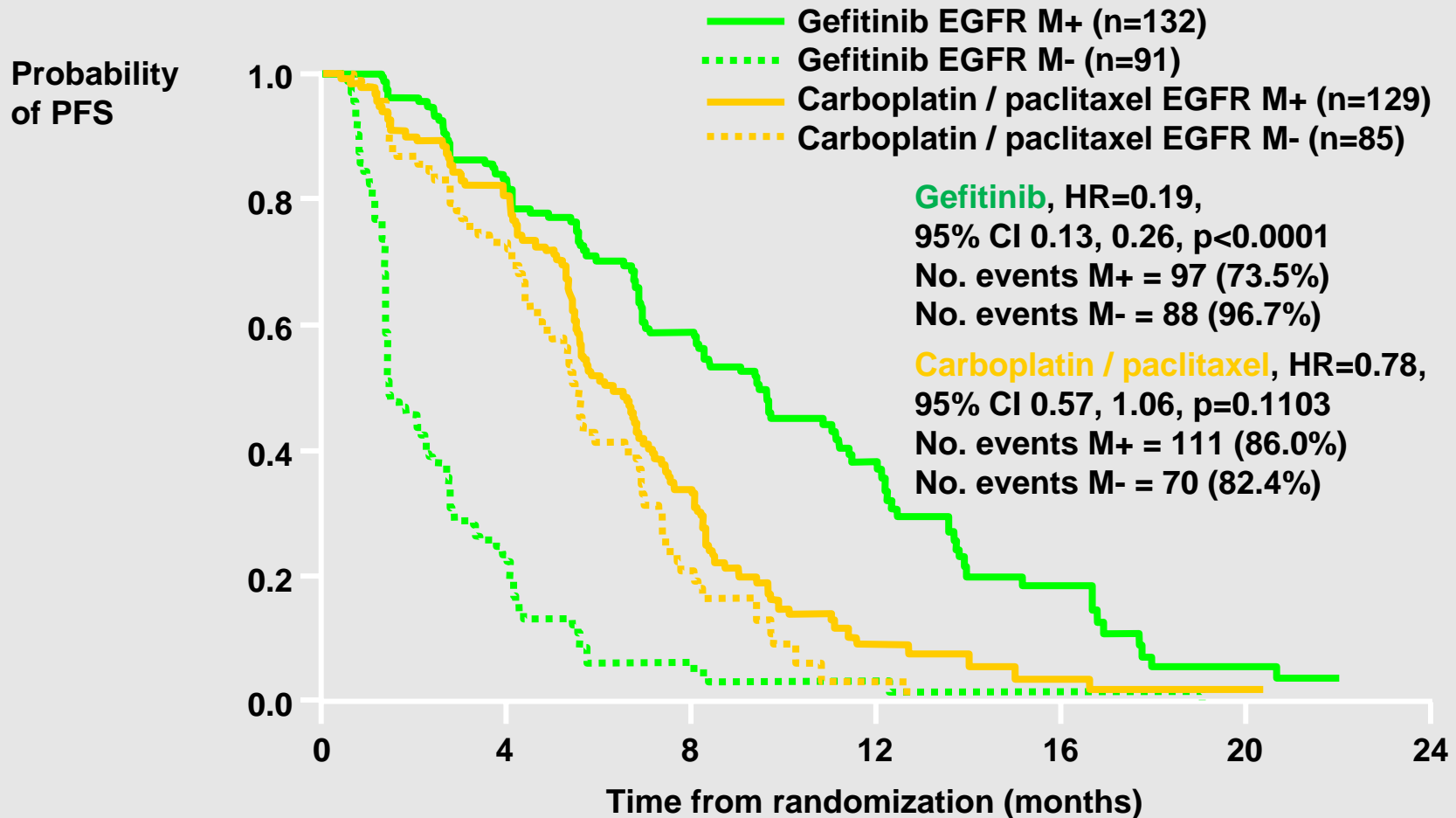
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D.,
Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A.,
Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D.,
Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib

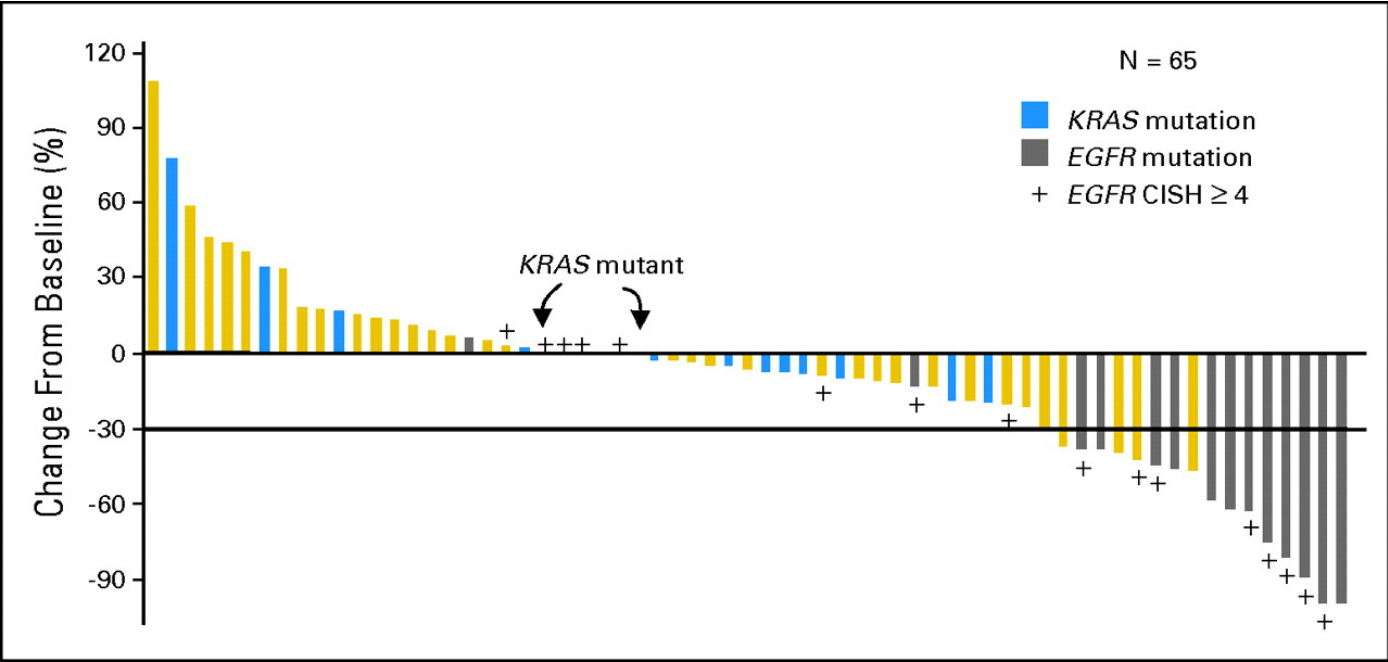
William Pao^{***}, Vincent Miller^{†§}, Maureen Zakowski[¶], Jennifer Doherty^{*}, Katerina Politi^{†*}, Inderpal Sarkaria[‡],
Bhuvanesh Singh[‡], Robert Heelan^{***}, Valerie Rusch[‡], Lucinda Fulton^{††}, Elaine Mardis^{††}, Doris Kupfer^{††}, Richard Wilson^{††},
Mark Kris^{†§}, and Harold Varmus^{*}

Comparison of PFS by mutation status within treatment arms



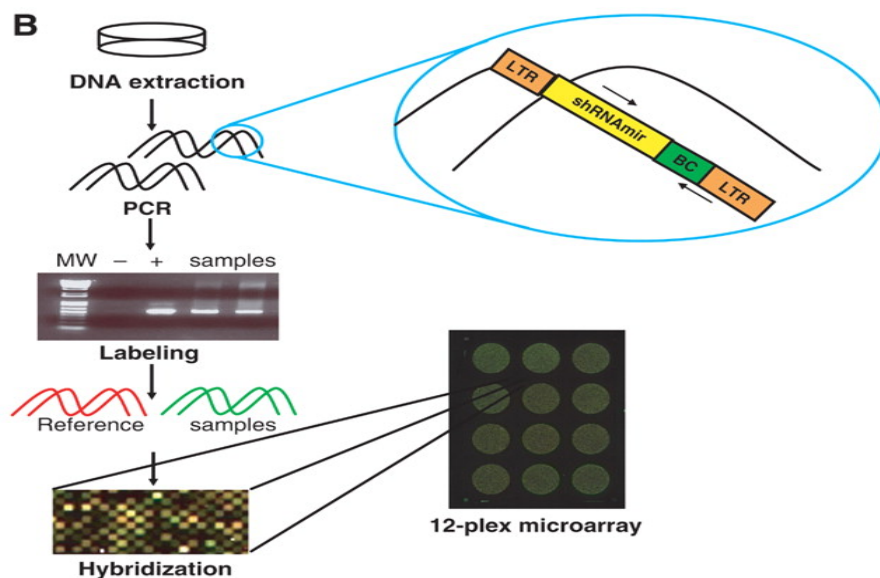
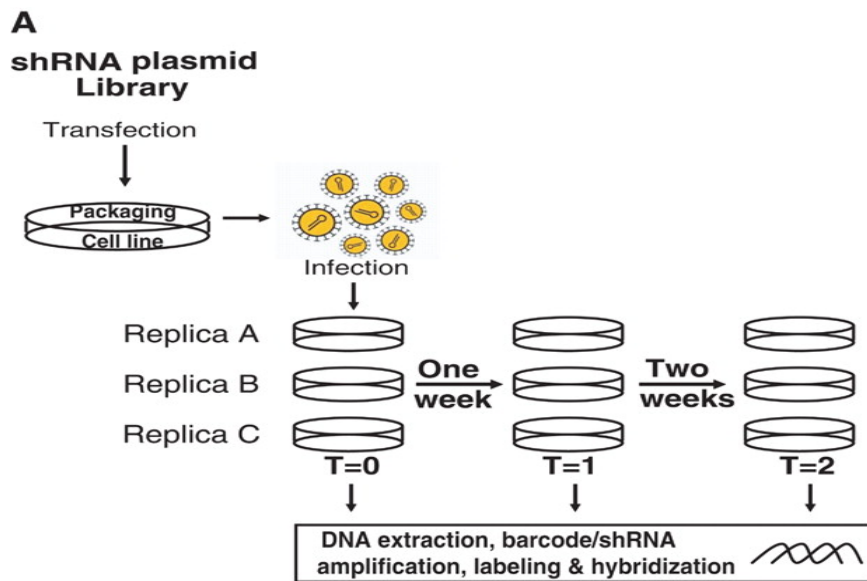
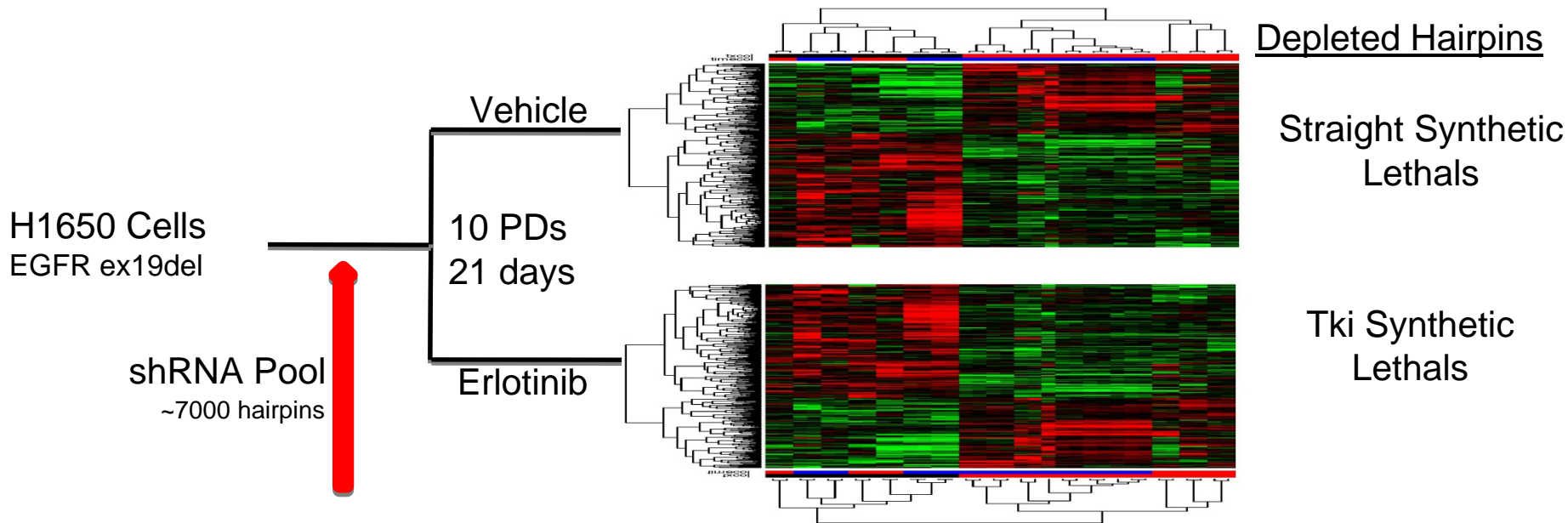
Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M- group

EGFR Mutation + Tumors Respond Variably to EGFR TKi

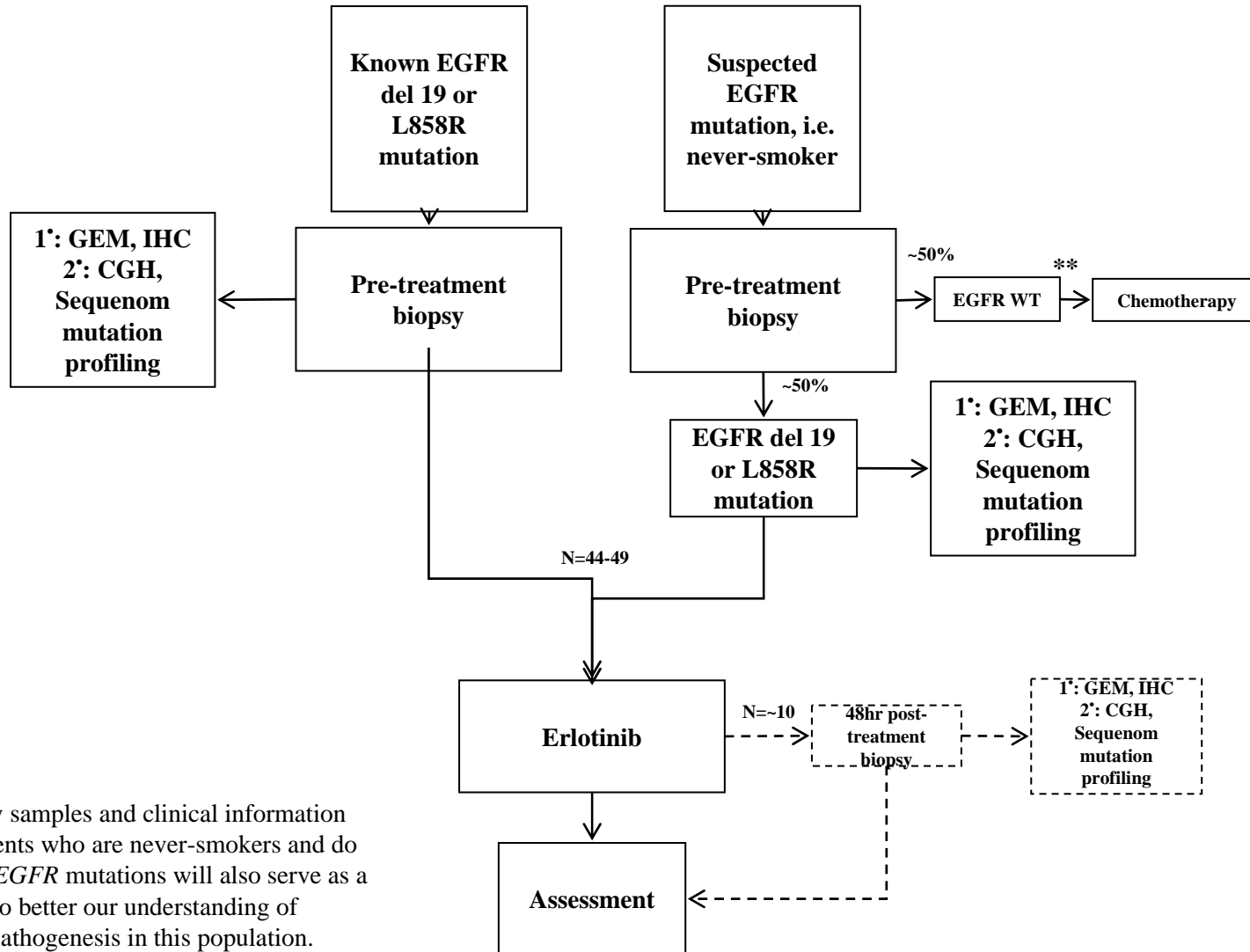


Miller, V. A. et al. J Clin Oncol; 26:1472-1478 2008

Functional Genomic Analysis Experimental Design



Molecular heterogeneity of EGFR mutant lung cancer: pre-treatment and post-treatment biopsy protocol



** Biopsy samples and clinical information from patients who are never-smokers and do not have *EGFR* mutations will also serve as a resource to better our understanding of NSCLC pathogenesis in this population.

Background and Hypothesis

- **Patients with CML and GIST have a high rate of response to treatment with imatinib.**
- **These patients commonly acquire resistance after an initial response.**
- **Virtually all patients with response to gefitinib or erlotinib eventually have progression of disease.**
- **We hypothesized similar “gatekeeper” or secondary mutations would be present upon rebiopsy in NSCLC patients with initial sensitivity to EGFR-TKIs and subsequent progression of disease.**

IRB Protocol # 04-103

Procedure

- **Two needle biopsies (when feasible) of most metabolically active site of disease**
 - **FNA w cell block 1:**
 - **Diagnostic Molecular Pathology for EGFR and T790M**
 - **Core 2 (snap frozen): gene expression**

Results: Biopsies (N=134) *

63 research biopsies

- IR guided core biopsies
 - 44 intrapulmonary
 - 12 extra pulmonary
- 1 lymph node excision
- 1 endoscopic ultrasound
- 5 bedside FNA
 - 3 lymph node
 - 1 pleural
 - 1 VP shunt

71 clinically required procedures

- 28 surgical biopsies
 - 7 lobectomies
 - 7 VATS biopsies
 - 6 brain metastectomies
 - 3 laminectomies
 - 5 other
- 11 minimally invasive biopsies
 - 7 IR guided biopsies
 - 2 kyphoplasties
 - 2 bedside FNA
- 32 fluid cytology samples
 - 22 Pleural fluid
 - 6 Lumbar punctures
 - 2 Peritoneal fluid
 - 2 Pericardial fluid

* 22 patients had multiple specimens studied (range 2-3), 7 patients not rebiopsied

Sample Adequacy

93% (94/101) surgical pathology and FNA samples were adequate for mutation analysis

- 6 biopsy samples were negative for mutations and had no tumor in the corresponding FFPE or aspirate
- 1 unsuitable for testing due to extensive radionecrosis

73% (24/33) fluid cytology samples adequate for mutation analysis

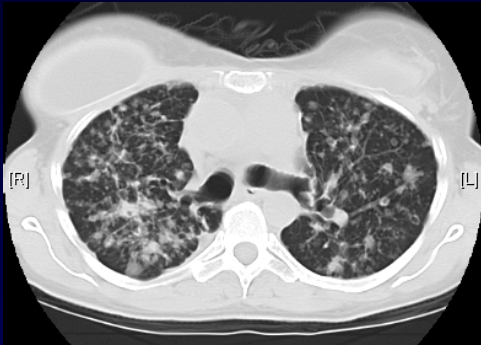
- 9 fluid cytology samples insufficient or degenerated

Mutation Correlation Between Baseline and Rebiopsy Specimens

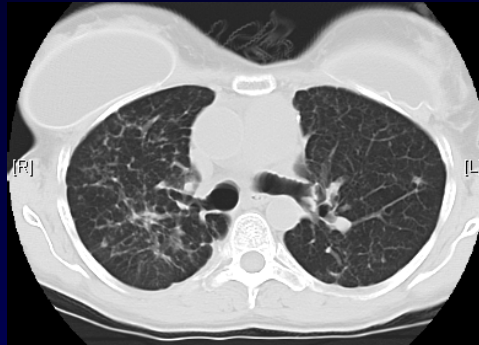
- **98% (54/55) paired samples retain the same sensitizing EGFR mutation**
 - 7 exact matches by sequencing
 - 54 matched by fragment analysis
 - 52 mutant EGFR
 - 2 EGFR WT (1 KRAS mutant)
- **1 case with EGFR exon 19 del pre-treatment was WT at recurrence (re-biopsy x 2)**

Acquired resistance to TKI

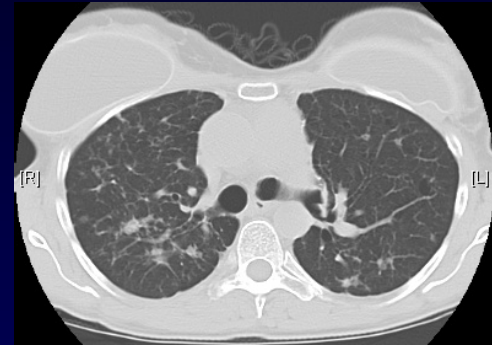
Baseline



4 mo



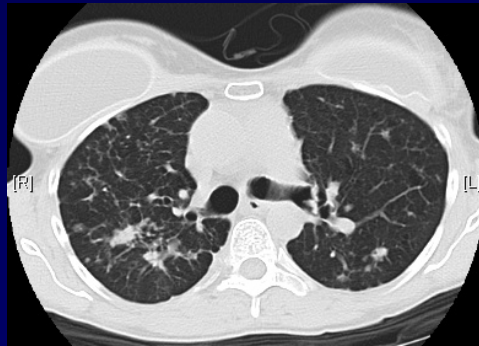
19 mo



21 mo



23 mo



25 mo



Bx

Biology of T790M

Clinical Correlate

Baseline



4 mo



19 mo



21 mo



23 mo



25 mo



Bx

T790M prevalence

- **T790M detected in 58 patients (62%)**
 - **T790M prevalence with LNA-sequencing estimated at 68%**

Site	N	% T790M
Lung/pleura	67	66%
Lymph node	6	75%
Liver	6	66%
Bone	4	25%
Brain	3	66%
Adrenal, uterine cervix, skin, peritoneum	5	20%

T790M as a biomarker

T790M-mediated resistance

- Longer survival
- Later metastases
- Indolent growth

- Sensitivity to 2nd line EGFR inhibitors?

Non-T790M resistance

- Poorer survival
- Earlier metastases
- More aggressive?

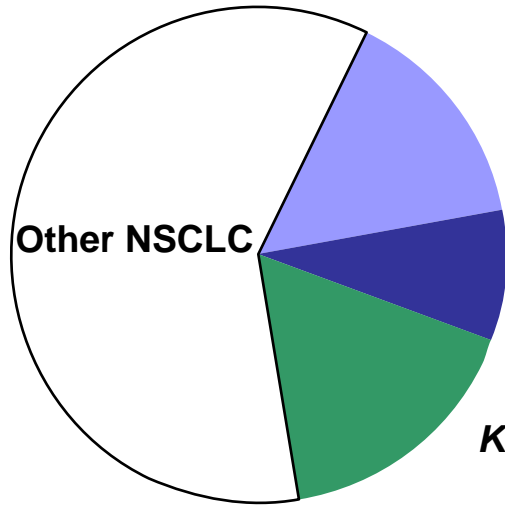
- Need to elucidate mechanisms better
- Alternate therapies?

Approach to Therapy of Acquired Resistance to EGFR-TKIs

- **Rebiopsy the patient**
 - T790M prognostic and possibly predictive biomarker
 - Rare transformation to small cell phenotype
- **Continue an EGFR-TKI**
- **“Second generation” EGFR/ErbB2 TKIs**
- **Rational combination strategies**
 - BIBW2992 + cetuximab
 - HSP-90 inhibitor + chemo or EGFR-TKI
 - Add MET inhibitor-best diagnostic unclear

Lung Cancer 2008 – USA

215,000 New Cases

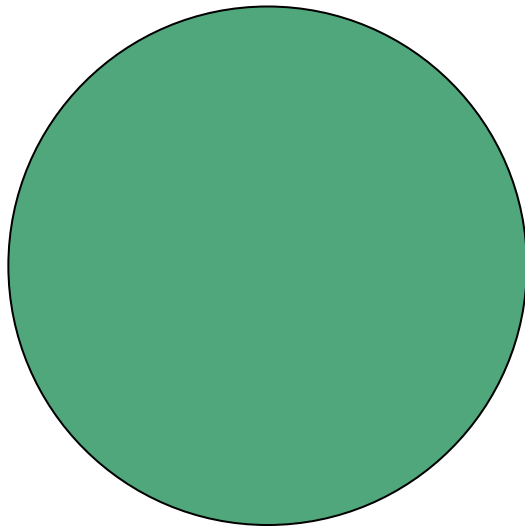


Small Cell Lung Cancer

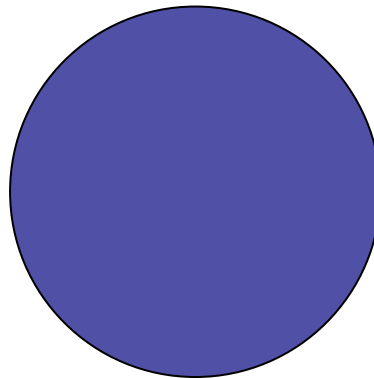
EGFR mutated (13% of NSCLC)

KRAS mutated (25% of Adenocarcinoma)

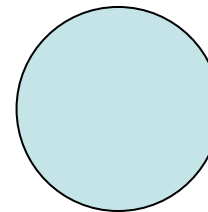
Relative Incidence of Some Oncogene Related Cancers



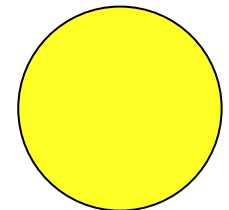
***KRAS*-mutated NSCLC**
29,000 cases/year



***EGFR*-mutated NSCLC**
15,000 cases/year



CML
4500 cases/year each



GIST

Conclusions

- **Identification of mutations in driver kinases in a significant number of lung adenocarcinoma has improved outlook for advanced disease.**
- **These treatments are not curative alone; rational combination therapies are needed. Mutations can serve as framework.**
- **Routine survey of pathway activation in addition to screening for mutant driver kinases is essential for next step forward.**
- **There is no blockbuster “targeted” drug for adenocarcinoma of lung rather blockbuster drugs for small % subsets.**

Acknowledgements

Thoracic Oncology Service

Geoffrey Oxnard

Mark Kris

Greg Riely

Melissa Johnson

Paul Paik

Talia Goldstein

Pao Lab

William Pao

Julie Chmielecki

Aviva Goel

Radiology

Steve Solomon

Michele Ginsberg

Thoracic Surgery

Valerie Rusch

Pathology

Marc Ladanyi

Maria Arcila

Laura Tafe & Snjezana Dogan

Maureen Zakowski

Cytogenetics:

Suresh C Jhanwar

Mamta Rao

Funding

NIH R21-CA11505-01

Joan's Legacy

Doris Duke Charitable Foundation

Carmel Hill Fund

ASCO Young Investigator Award