Personalized Therapy for Advanced NSCLC: Lessons Learned from BATTLE

Roy S. Herbst, MD, PhD
Chief of Medical Oncology
Associate Cancer Center Director for Translational Research

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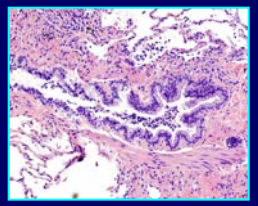
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

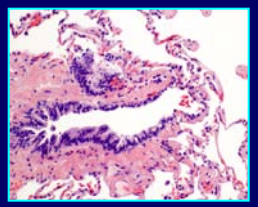
SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Multiple Pathways of Lung Adenocarcinoma Pathogenesis ("Driver Mutations")

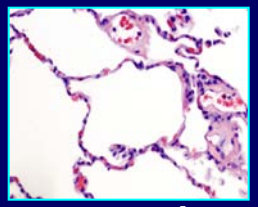
Origin of Adenocarcinoma



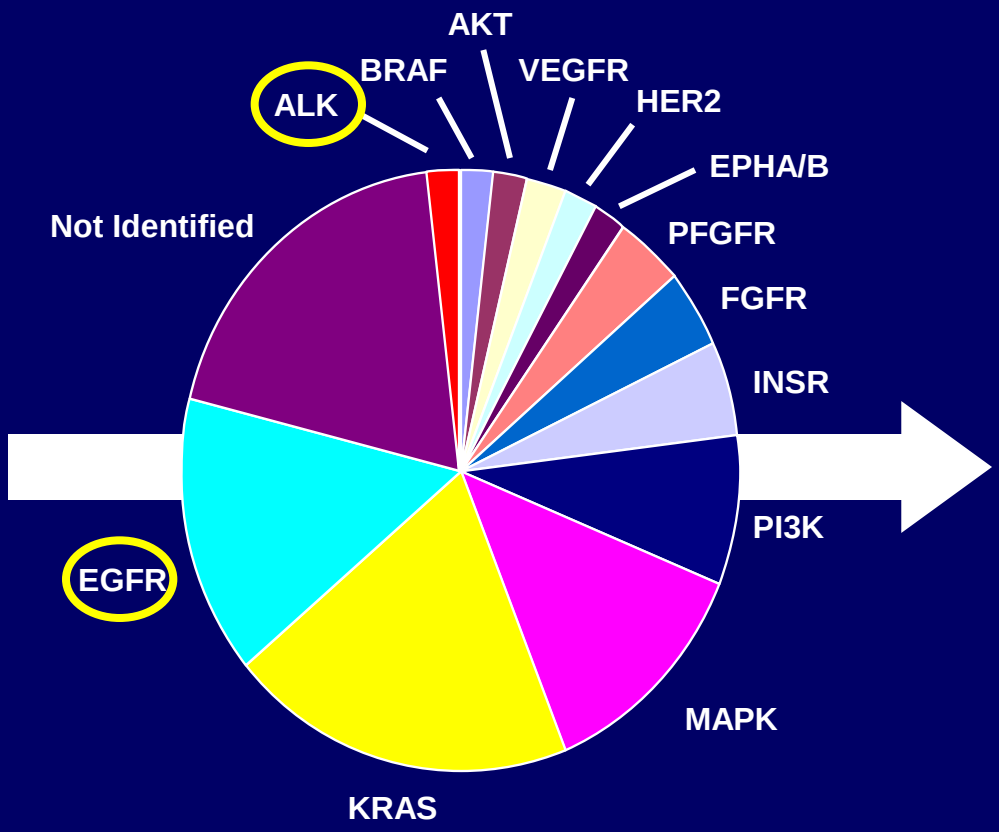
Normal Small Bronchus



Normal Bronchiole

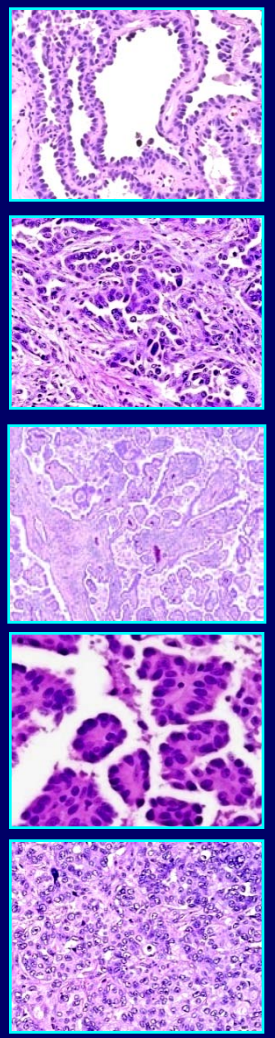


Normal Alveoli



Mutation analysis of 188 tumors and sequencing of 623 genes

Adenocarcinoma

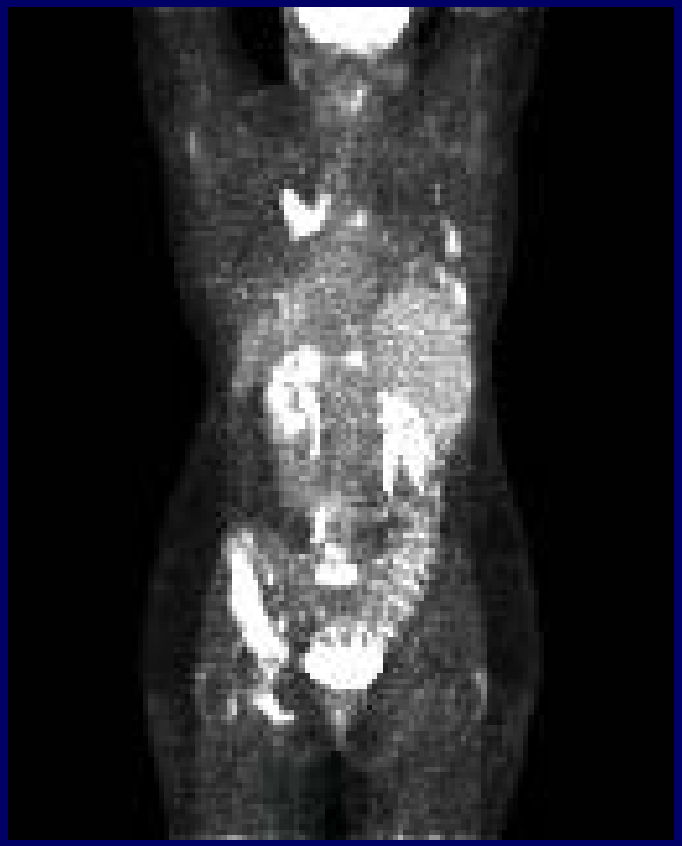


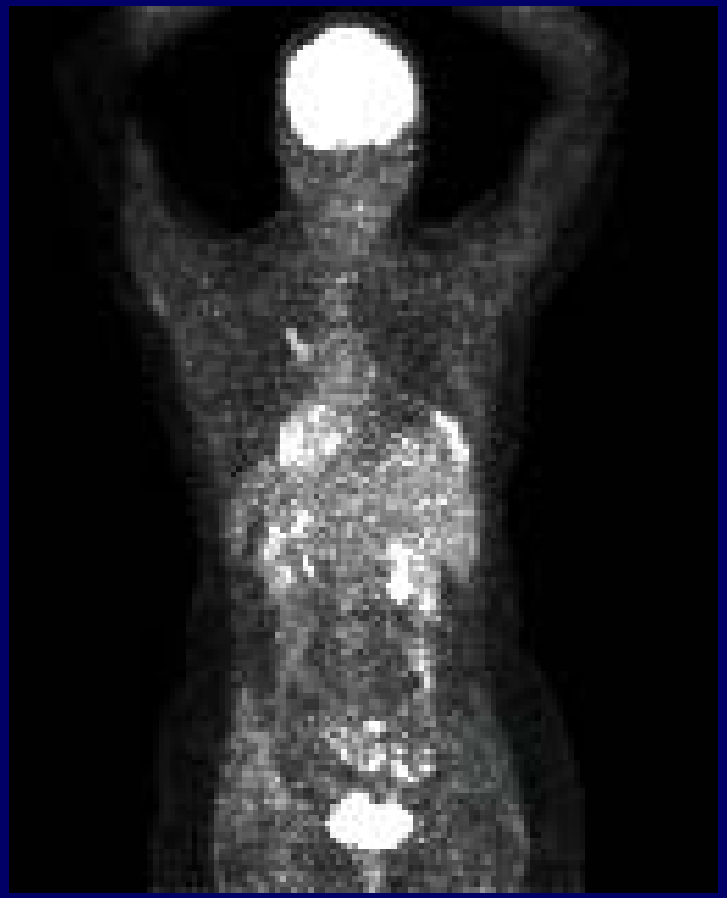
Adapted from Ding et al, Nature 455:1069, 2008

Never Smoking 50yo Woman Treated with Single Agent Erlotinib as First Line Therapy for NSCLC

(Deletion in Exon 19)

10-14% of US patients

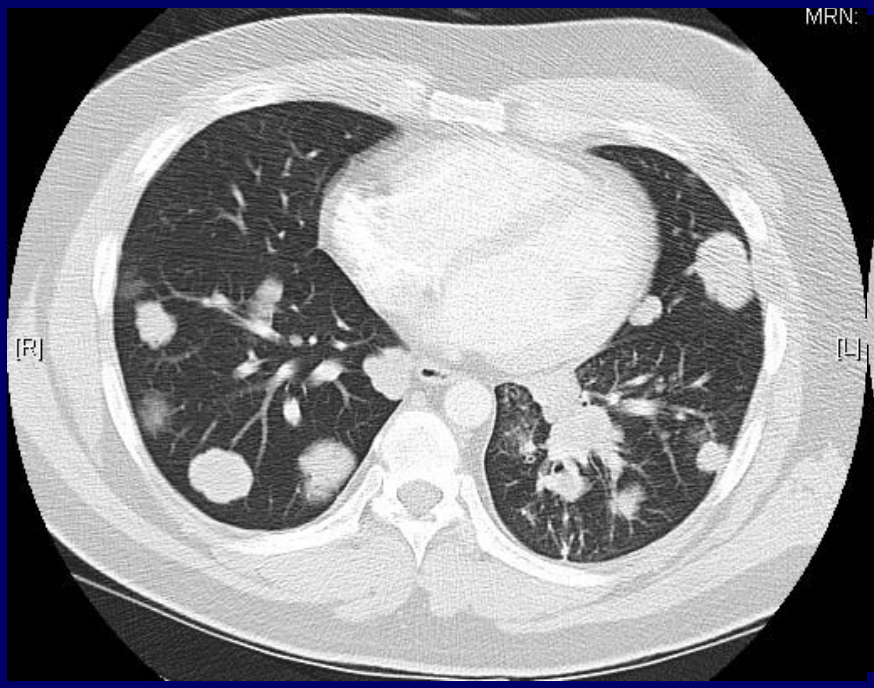




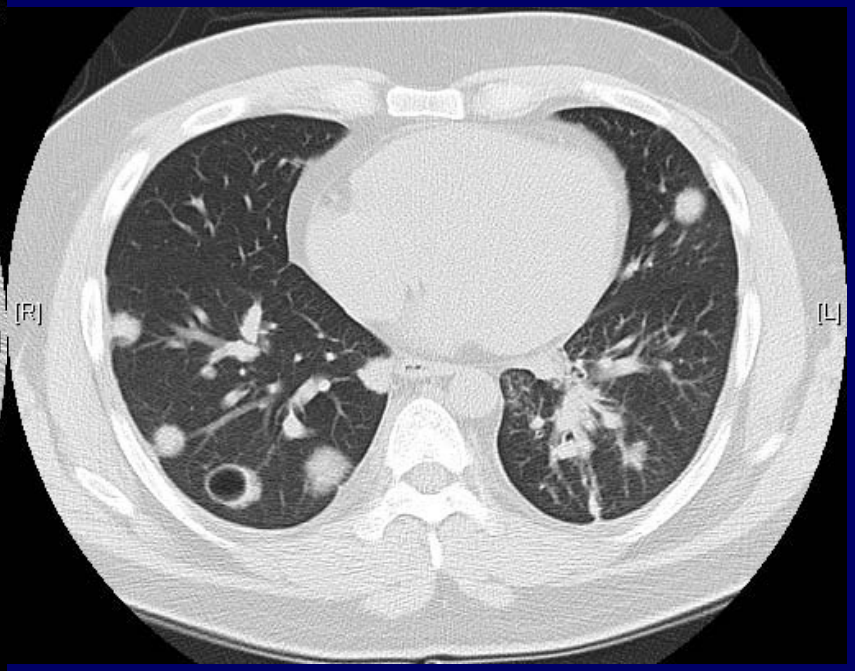
August 2005

November 2005

Response after 40 days with Crizotinib (PF-02341066): *EML4-ALK* Fusion Gene



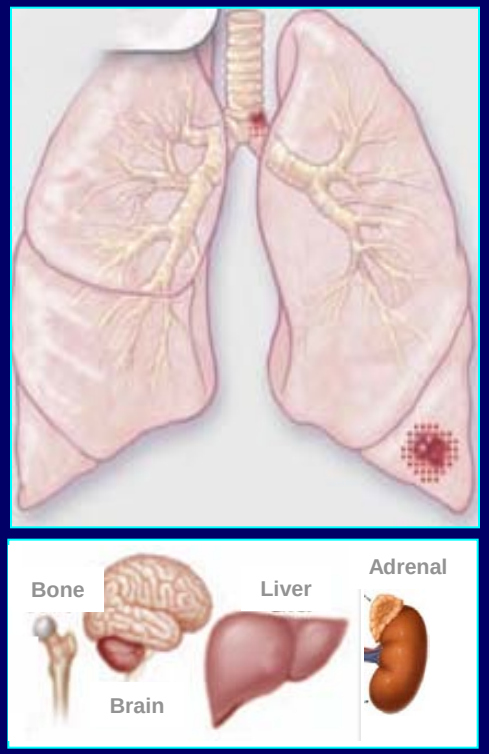
Baseline

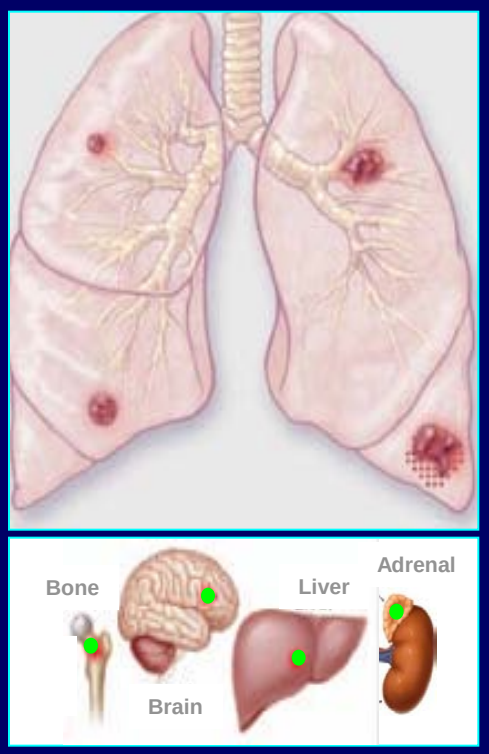


40 days after PF-02341066

Natural History of Lung Cancer

Stages I-III Surgically Resected	Advanced – Stage IV Untreated	Advanced - Stage IV Refractory to Chemotherapy





Tissues Available	Frequent	Infrequent	Rare

Adapted from Herbst et al, N Engl J Med 359:1367, 2008

What is BATTLE?

***B*iomarker-based *A*pproaches of *T*argeted *T*herapy for *L*ung Cancer *E*limination**

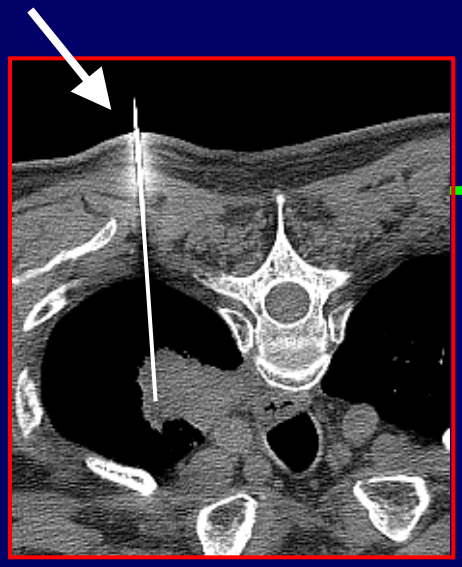
- Platform for integrated translational research
  - Clinical trial program
  - Novel trial design
  - Biomarker discovery
- Scientific Hypotheses
  - Real time biopsies are possible to more accurately reflect aberrant signaling pathways of lung cancer
  - Matching targeted agents with abnormal pathways will improve disease control in lung cancer patients
  - 8-week disease control is an acceptable surrogate for efficacy in patients with pretreated lung cancer

BATTLE Eligibility Criteria

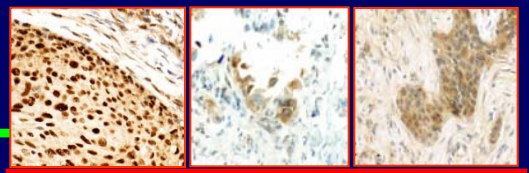
- 2nd + Line non-small cell lung cancer
  - Heavily treated population
- Adequate performance status
  - ECOG PS 0-2
- Biopsy-amenable disease
  - Required 2 fresh core biopsies
- Stable brain metastases allowed

BATTLE Schema

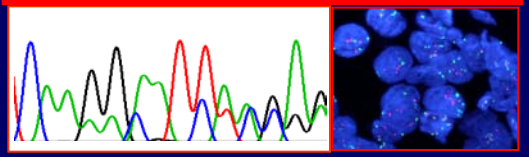
Umbrella Protocol



Core Biopsy



Biomarker Profile



EGFR KRAS/BRAF
VEGF RXR/CyclinD1

Randomization:

Equal → Adaptive

- Erlotinib
- Vandetanib
- Erlotinib + Bexarotene
- Sorafenib

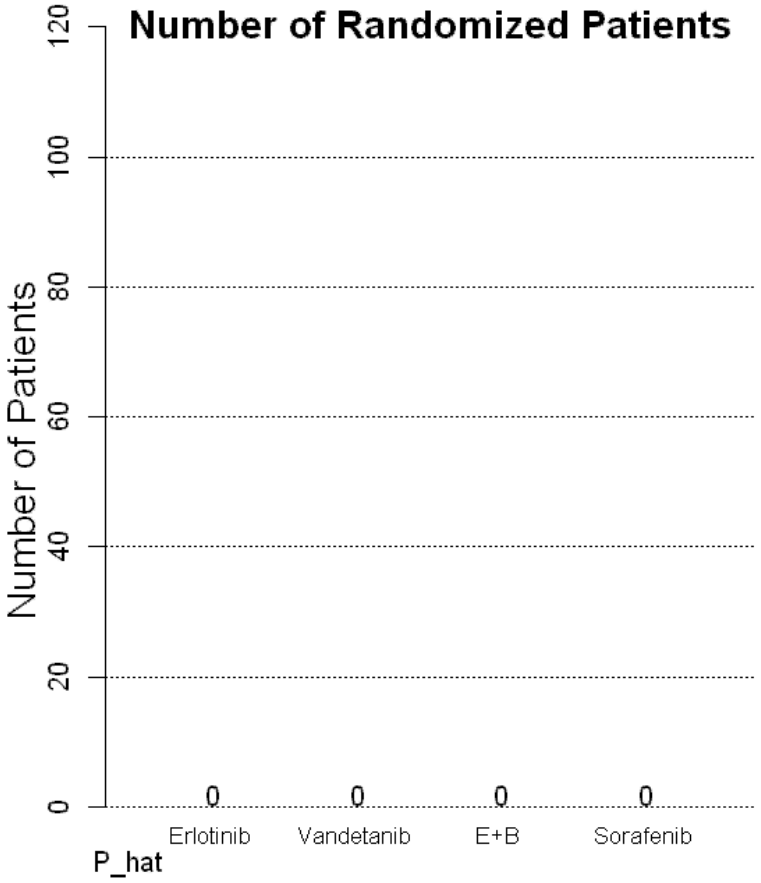
Primary end point: 8 week Disease Control (DC)

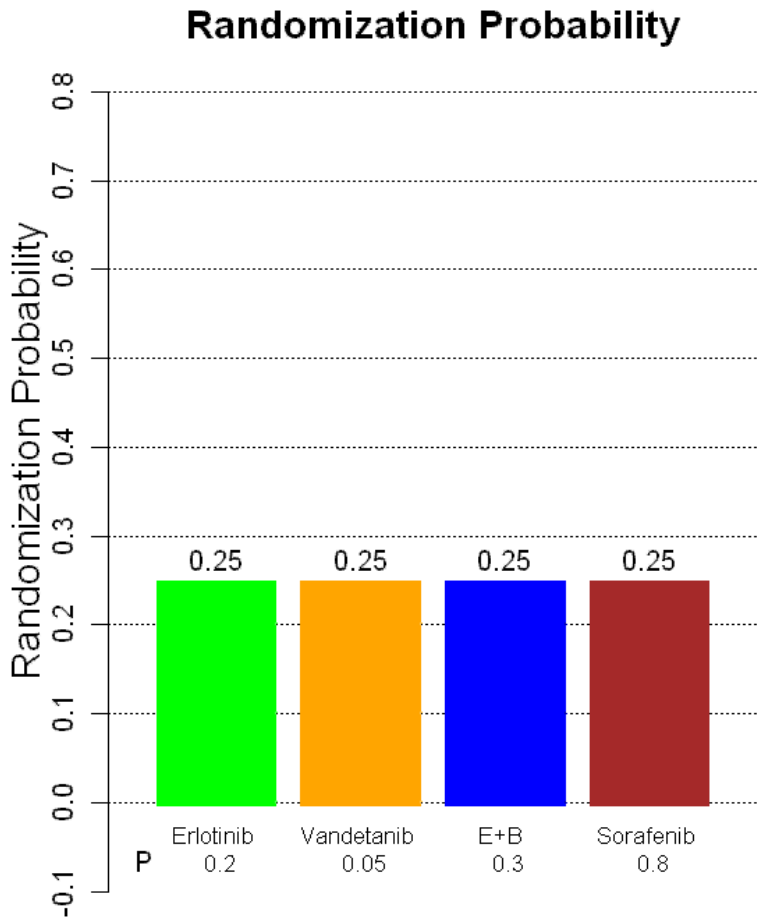
Bayesian Adaptive Randomization:

- More patients are assigned to more effective therapies
- Based on accumulating patient data
- We learn as we go!
- Success *dependent* on good biomarkers guiding assignments to good treatment options

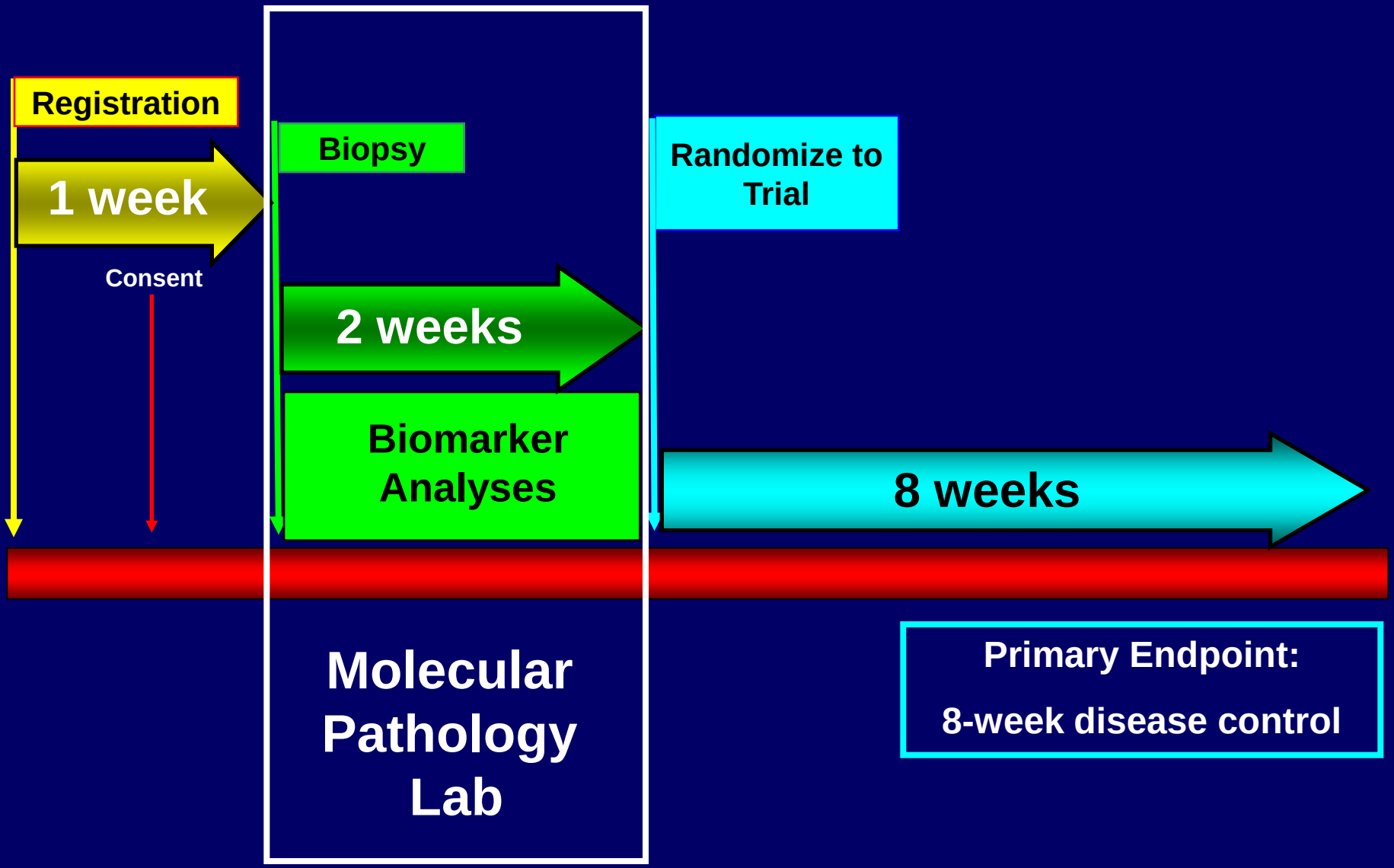
Example of Adaptive Design Models After Data in K-ras, B-raf Marker Group

ER: Patient Number: 0





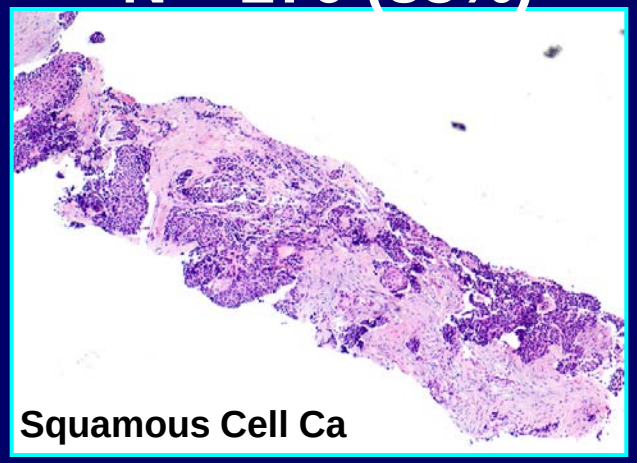
BATTLE Patient Evaluation Schema

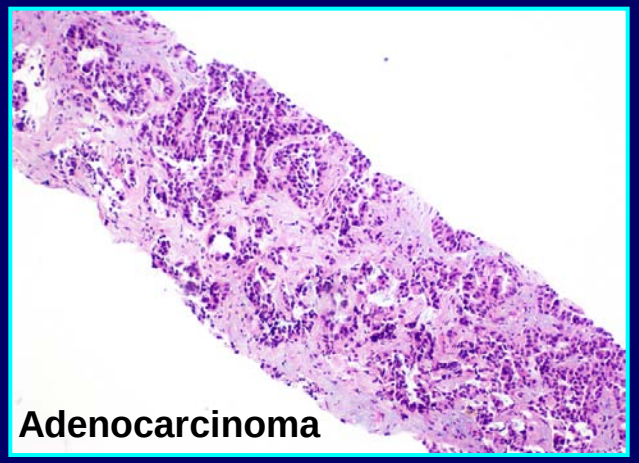


BATTLE: Tissue Specimens for Biomarker Analysis - Core Needle Biopsy (CNB), N=324

Adequate Biopsies:

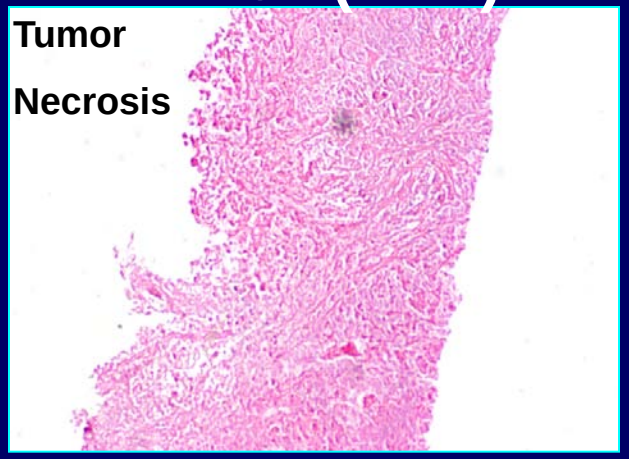
N = 270 (83%)

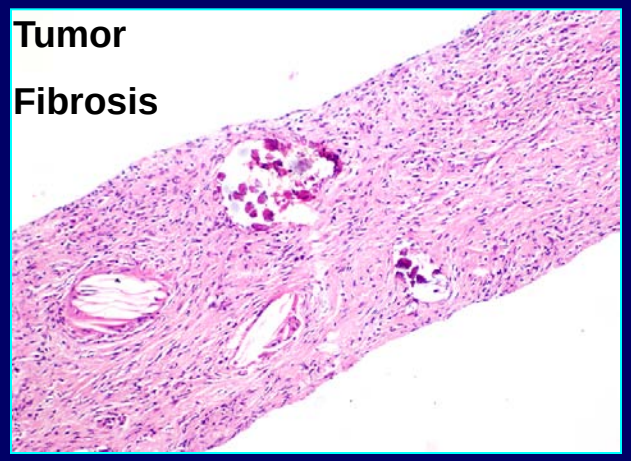




Inadequate Biopsies:

n = 54 (17%)





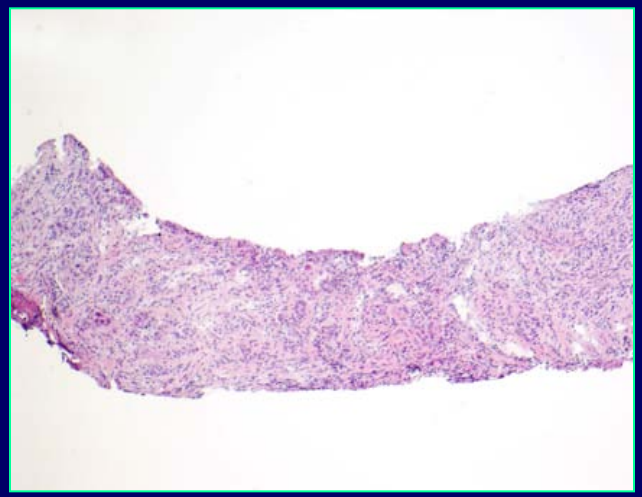
Individual Biomarkers for Response and Resistance to Targeted Treatment: Exploratory Analysis

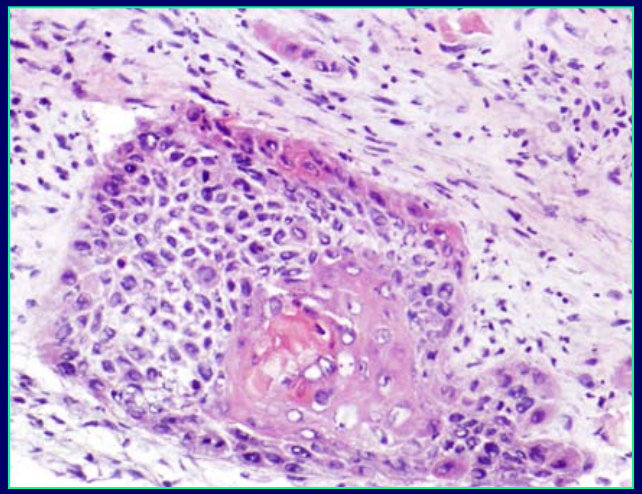
Drug Treatment	Biomarker	P–value	DC
Erlotinib	*EGFR* mutation	0.04	Improved
Vandetanib	High VEGFR-2 expression	0.05	Improved
Erlotinib + Bexarotene	High Cyclin D1 expression	0.001	Improved
	EGFR FISH Amp	0.006	Improved
Sorafenib	*EGFR* mutation	0.012	Worse
	EGFR high polysomy	0.048	Worse

BATTLE Trial: Discovery

- Fresh frozen tissue specimens: mRNA profiling (Affymetrix) and Proteomic RPPA

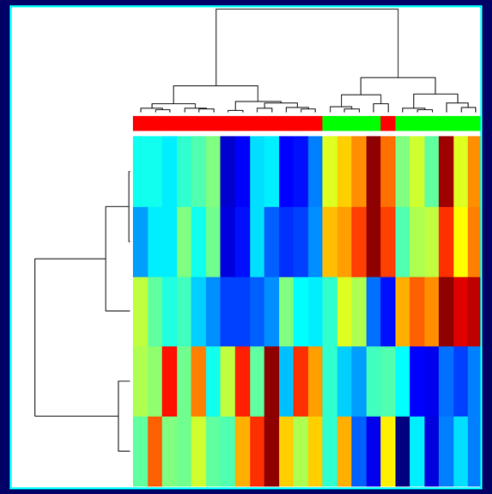
CNB - Frozen





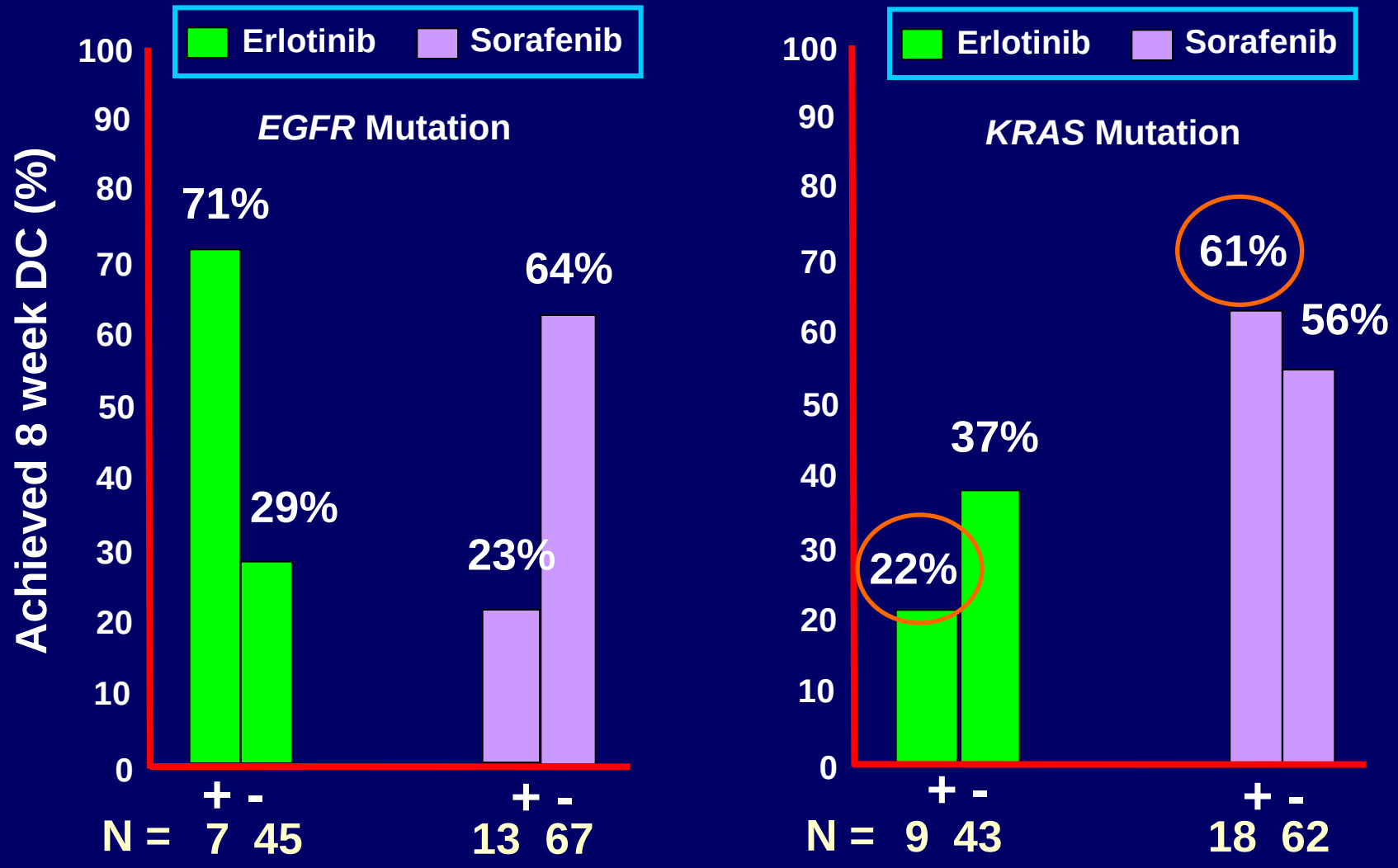
Squamous Cell Carcinoma

mRNA Profiling

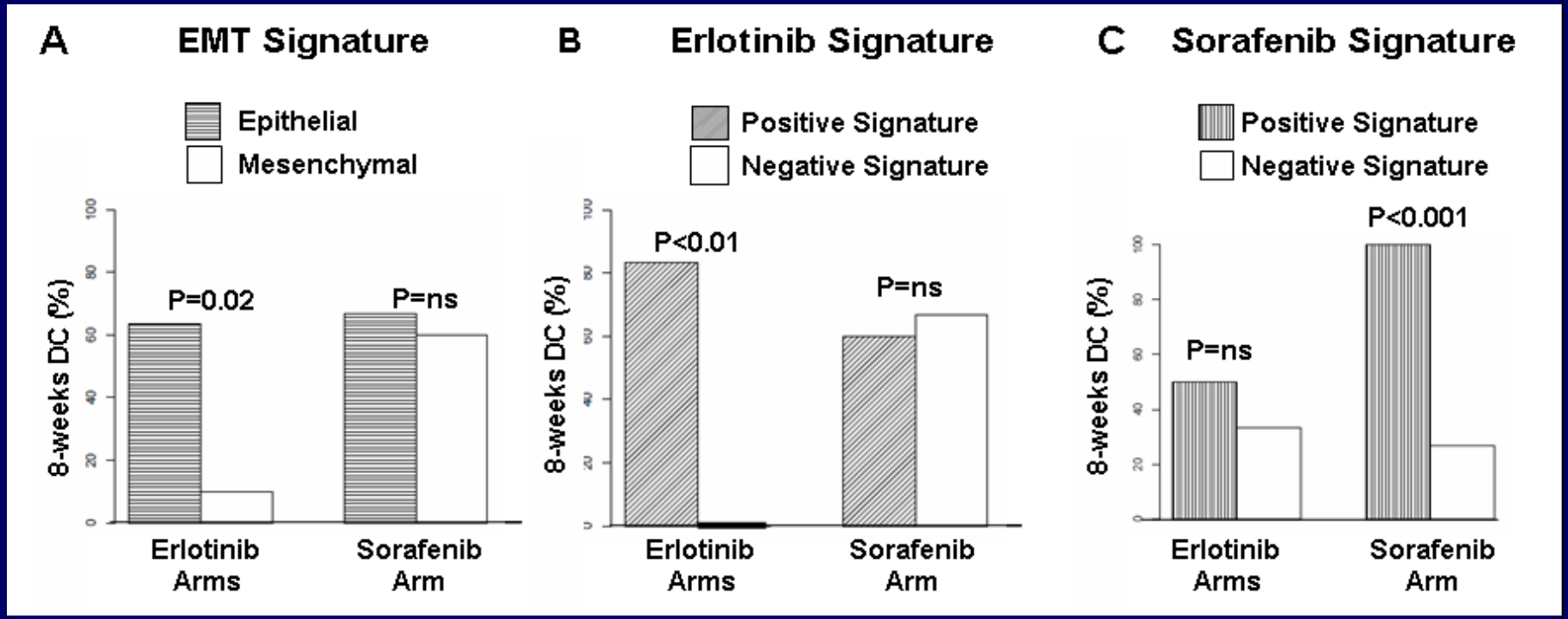


5-Gene Erlotonib Signature

EGFR and *KRAS* Mutations: Novel Discovery Findings

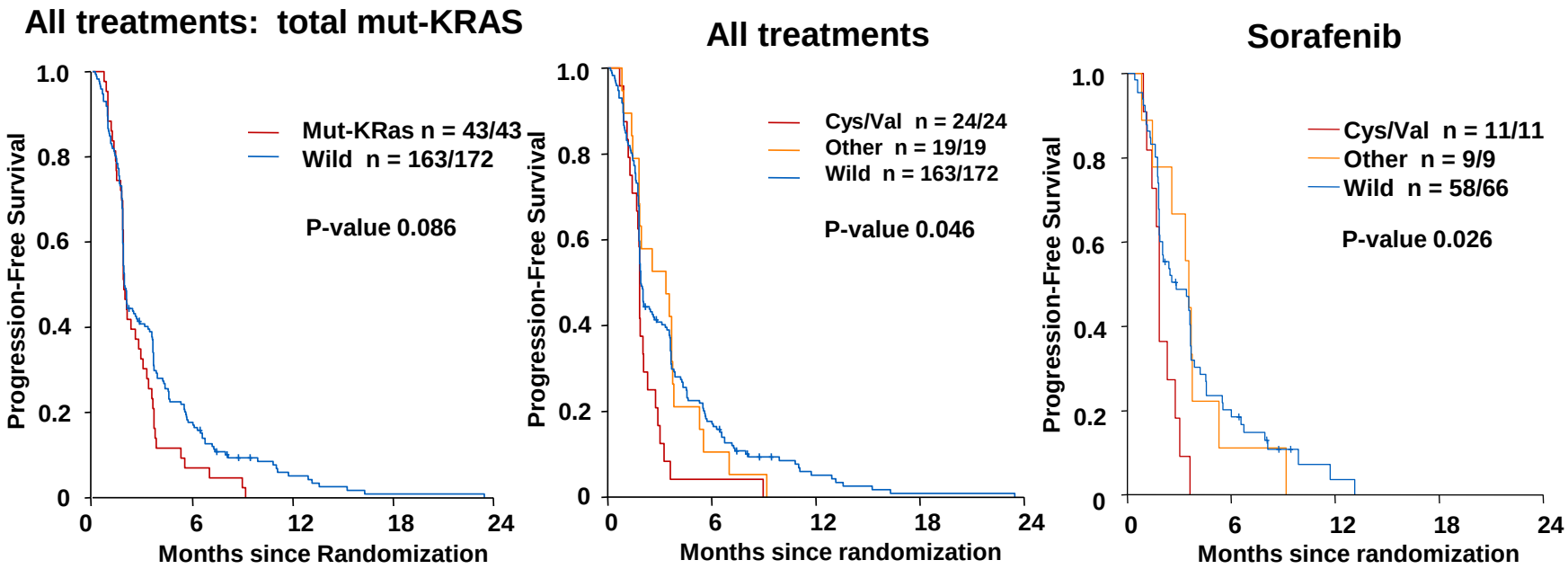


Gene Signature Development from the BATTLE-1 Trial



Heymach al, AACR 2011

BATTLE-1 Progression Free Survival



Median PFS	
mut-KRas (all)	1.91 month
wt-KRas	1.87 month

Median PFS	
mut-KRas Cys/Val	1.84 month
other mut-KRas	3.35 month
wt-KRas	1.95 month

Median PFS	
mut-KRas Cys/Val	1.84 month
other mut-KRas	3.55 month
wt-KRas	2.83 month

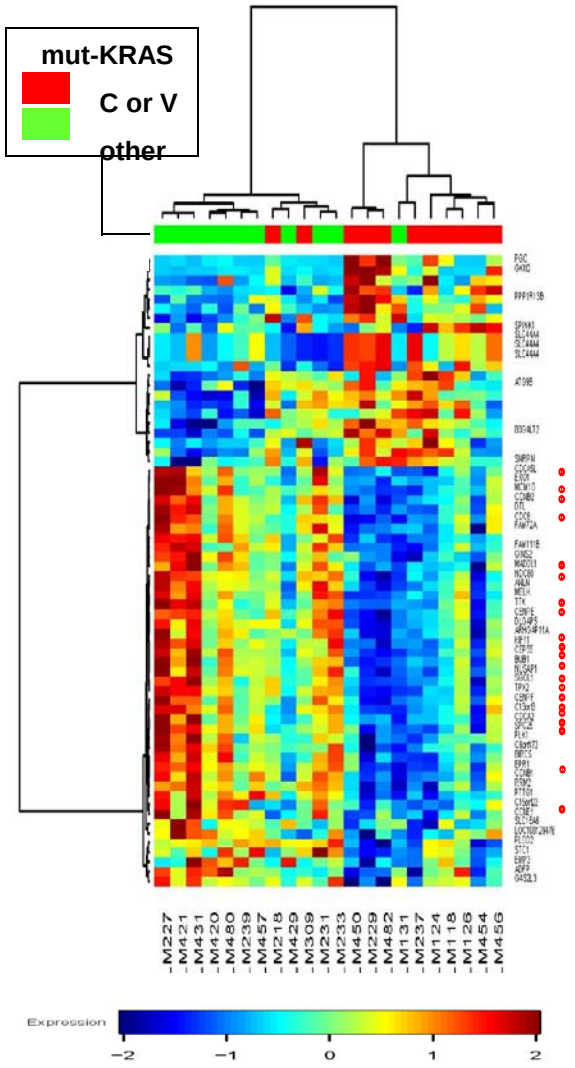
smokers Cys (50%), Asp (21%), Val (20%), Arg (4%)

never-smokers Asp (83%)

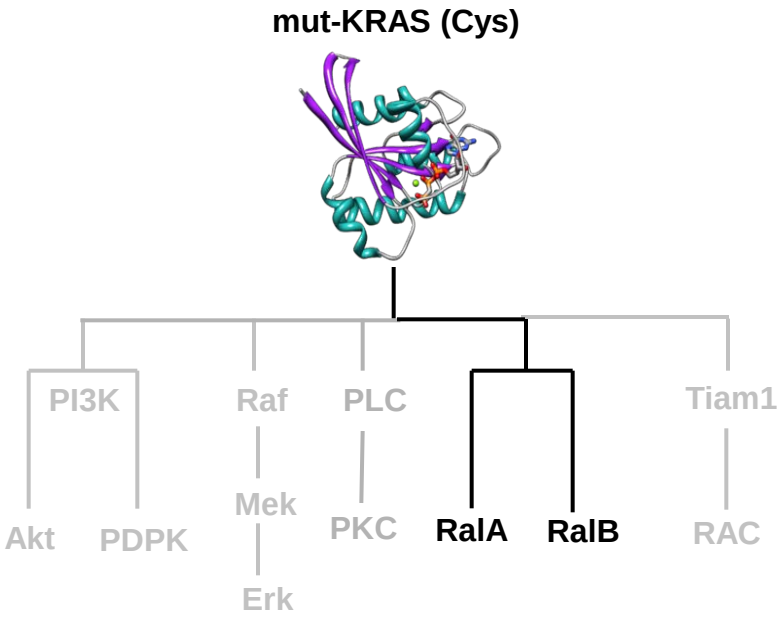
Colon Cys (8%), Asp (50%), Val (28%), Arg (4%)

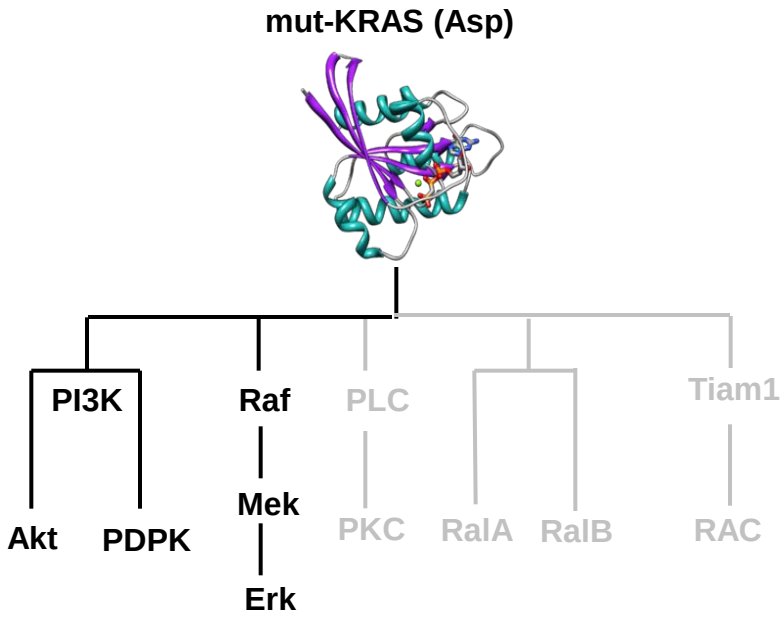
Microarray data from patients treated in BATTLE-1 trial

Clustering analysis of genes which most accurately define the differences between of two mut-KRas groups



Ihle et al, AACR 2011


mut-KRAS (Cys)
PI3K
Raf
PLC
Tiam1
Akt
PDPK
Mek
PKC
RalA
RalB
RAC
Erk


mut-KRAS (Asp)
PI3K
Raf
PLC
Tiam1
Akt
PDPK
Mek
PKC
RalA
RalB
RAC
Erk

Acknowledgements

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Suzanne Davis

Suyu Liu

Jeffrey Lewis

Ximing Tang

David Stewart

Merrill Kies

Marshall Hicks

Sanjay Gupta

Mellanie Price

Jeanne Riddle

Carmen Behrens

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William William

Jeremy Erasmus

Jennifer Ferguson

James Hall

Donald Berry

James Abbruzzese

Gabriel Hortobagyi

Jonathan Kurie

Frank Fossella

Charles Lu

Ralph Zinner

Daniel Karp

V. Papadimitrakopoulou

Bonnie Glisson

Kathy Pisters

Faye Johnson

Beverly Peeples

Alda Tam

Courtney Tyne

Carmen Martinez

Ganene Steinhaus

Linda Harrington

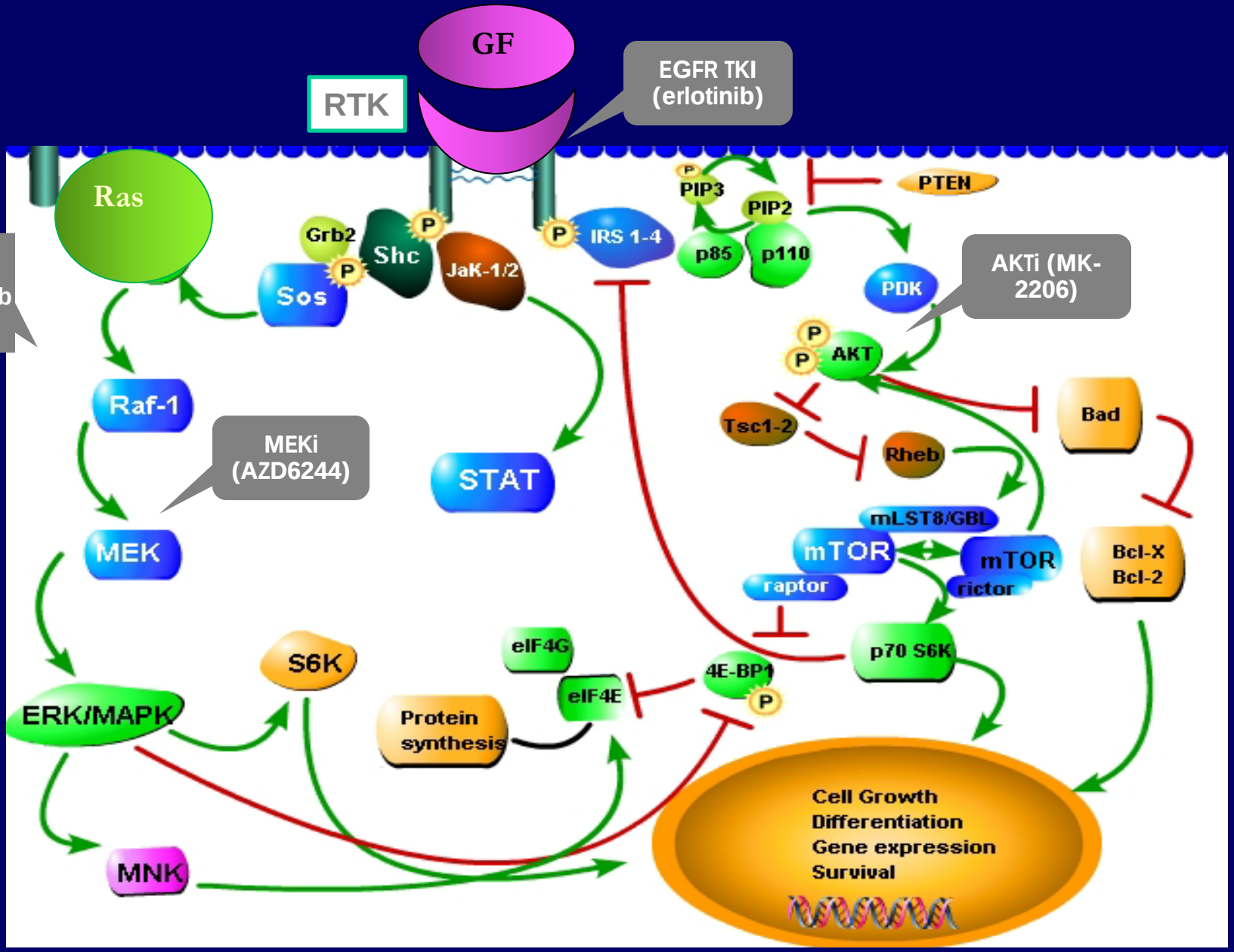
Pharmacists

APNs

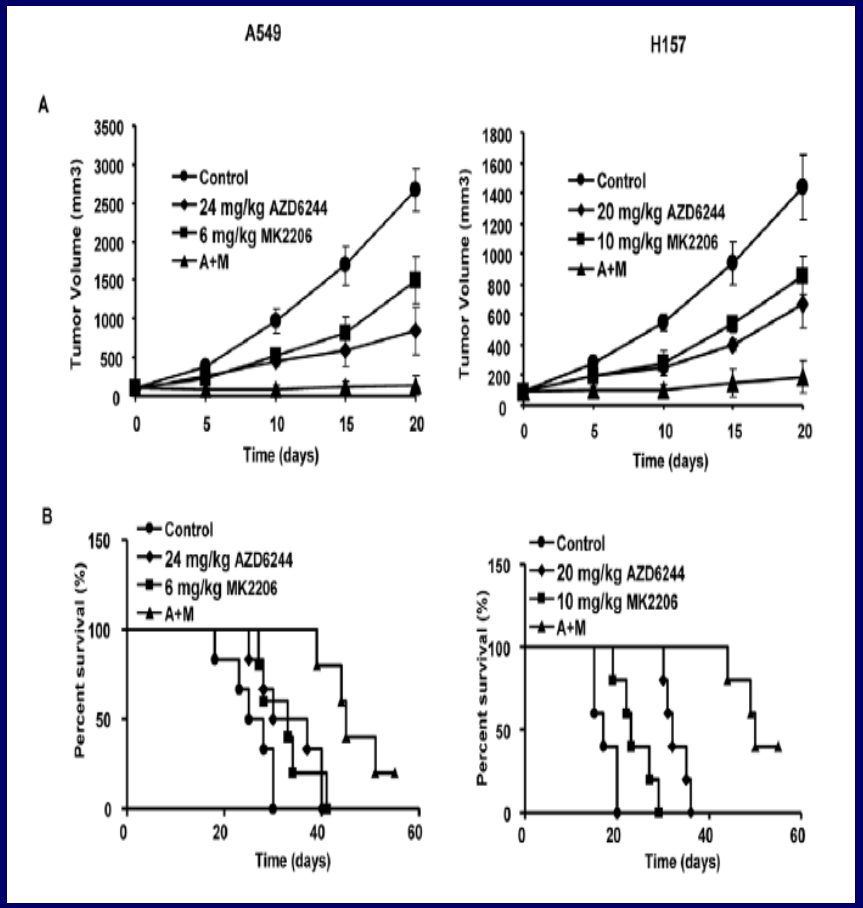
BATTLE-2
Lessons Learned: Building On Past Experience

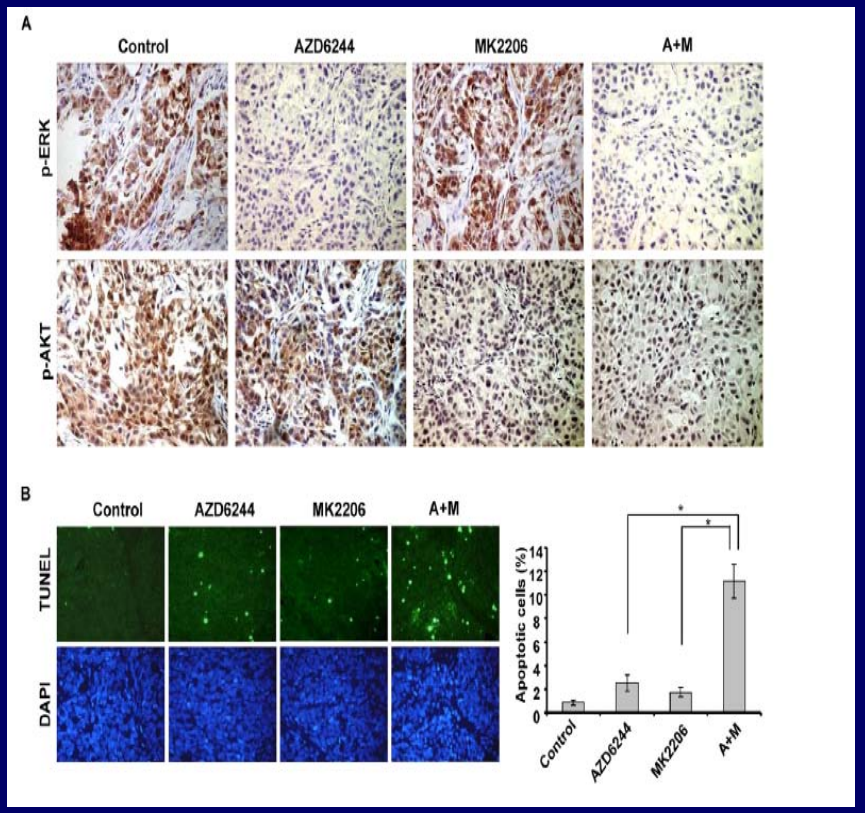
- Attempt to use more specific targeted drugs
- Attack more novel targets
- Drug Combinations
- Avoid biomarker grouping
- Selection and validation of novelme predictive biomarkers in real time
- Collaboration with Merck, AstraZeneca and Bayer/Onyx

Pathways Targeted IN BATTLE-2



Combination Treatment with MEK and AKT inhibitors



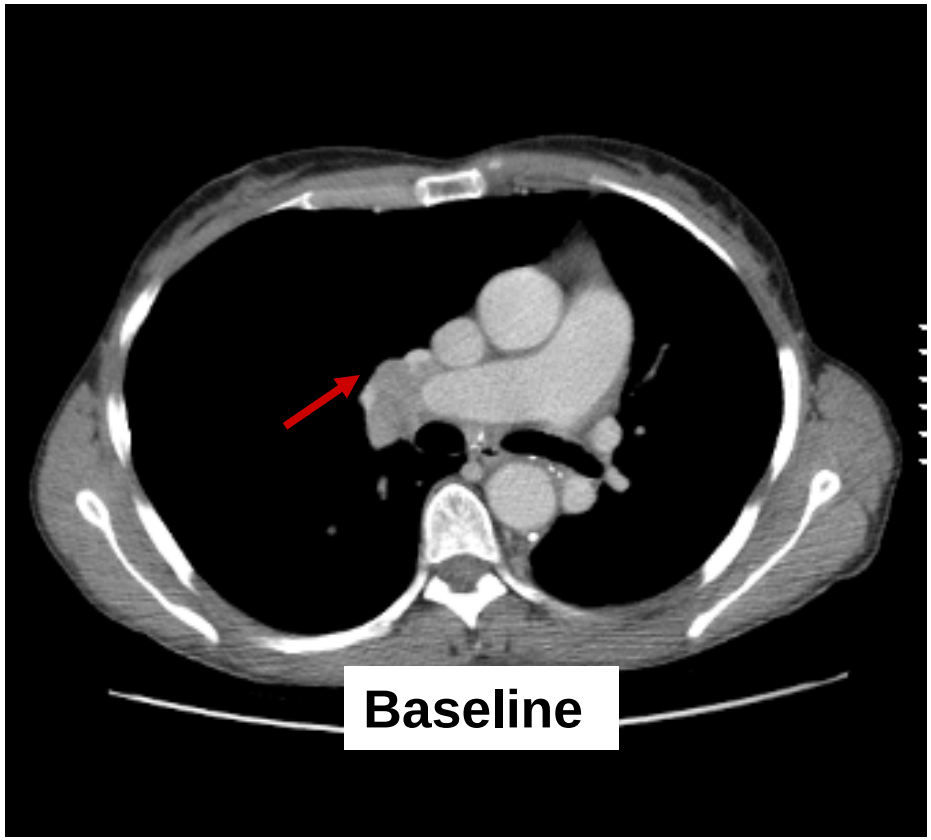


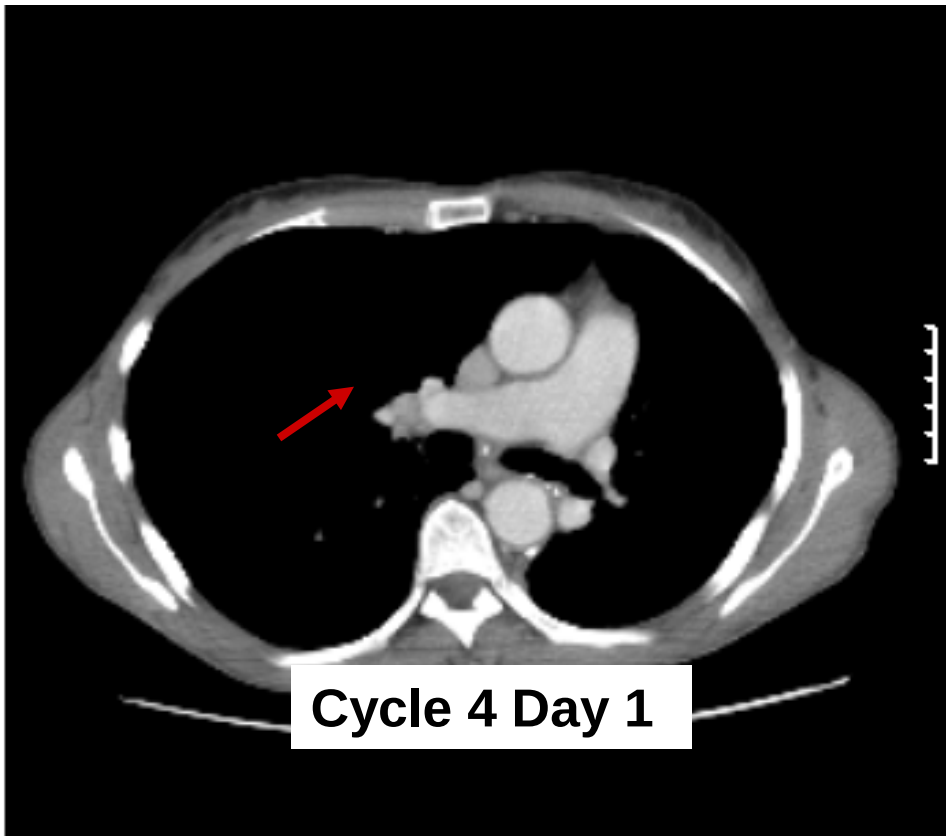
MDACC-AZ Alliance

Meng J et al.One , 2010

Tolcher et al, ASCO 2011

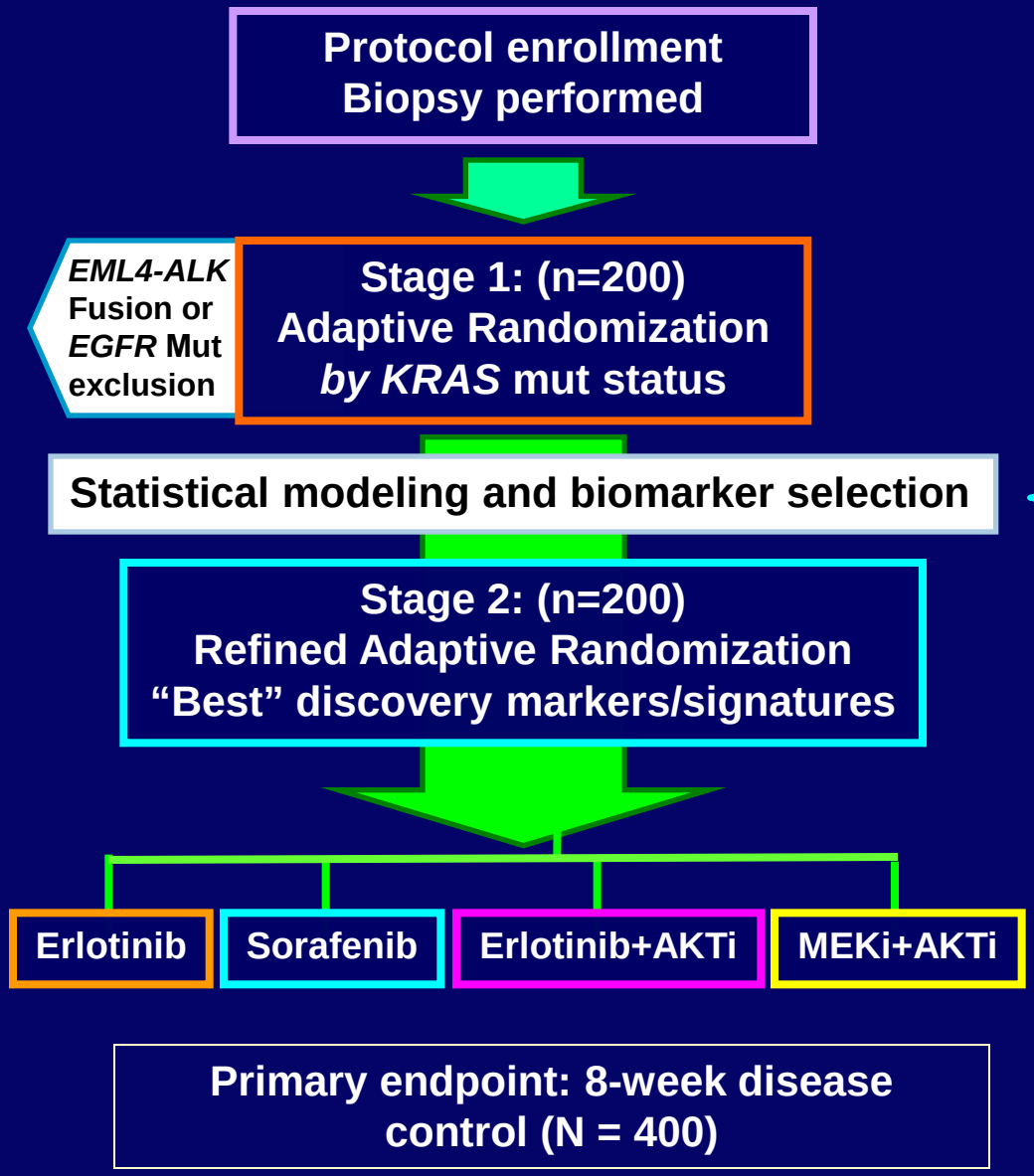
A phase I dose escalation study of
oral MK-2206 (allosteric AKT inhibitor)
with oral selumetinib (AZD6244; ARRY-142866) (MEK inhibitor) in patients
with advanced or metastatic solid tumors . Tolcher AW et al, ASCO 2011, abstr#77652, NCT01021748





NSCLC KRAS Mutant, PR after Course 2

BATTLE-2 Schema



Discovery Markers:

- **Protein expression (IHC):** FOXO3A, nuclear EGFR, p-AKT (Ser473), PTEN, HIF-1α, LKB1
- **Mutation analysis (Sequenom):** *PI3KCA*, *BRAF*, *AKT1*, *HRAS*, *NRAS*, *MAP2K1* (*MEK1*), *MET*, *CTNNB1, STK11* (*LKB1*)
- **mRNA pathways activation signatures: Affymetrix®**
  - BATTLE-1: WT-*EGFR*-Erlotinib, EMT, and Sorafenib
  - BATTLE-2: new "discovery" signatures
- **Protein profiling – RPPA** (n=174)

BATTLE-2 Team














BATTLE-2 1: Personalizing NSCLC Therapy

Challenges for Personalized Therapy

- Requires significant resources
  - Multidisciplinary personnel
    - Medical/surgical oncologists
    - Interventional radiology
    - Research nursing personnel
    - Tissue/serum bank personnel
    - Molecular/clinical pathologists
    - Biostatistics/bioinformatics
    - Genomic and Proteomic Lab
  - Infrastructure
    - Pathology lab for biomarker analysis and assay development
  - Funding: Estimated >$20,000 per pt for biopsy-driven trials
- Integration between research and diagnostic CLIA-certified labs (need to develop new CLIA tests)
- Academic recognition of team effort
- Collaboration between academia and industry
- Regulatory Challenges