PARTNERING FOR CURES

A FasterCures Meeting

DESIGN OF A DISEASE SPECIFIC MASTER PROTOCOL

FRIENDS of CANCER RESEARCH

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FOUNDATION MEDICINE

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Current Challenges

- Each potential new therapy is typically tested independently from other therapies seeking to treat the same condition
- For every new trial, the protocol must be reviewed by a number of oversight entities
  - New phase III trials requires an average of 36 administrative or regulatory approvals and averages more than 2 years
- Approximately 4% of adult cancer patients enroll in clinical trials
  - Inability to meet accrual goals is a frequent factor causing trials to close, wasting time, money, and limited patient resources
- New therapies molecularly targeted against specific mutations may be present in only a fraction of the patient population

Design of a Disease-Specific Master Protocol

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2012 Friends/Brookings Conference on Clinical Cancer Research

ISSUE BRIEF

Conference on Clinical Cancer Research

November 2012

Design of a Disease-Specific Master Protocol

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center
Eric Rubin, Vice President, Clinical Research Oncology, Merck
Lisa LaVange, Director, Office of Biostatistics, CDER, FDA
Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI
David Wholley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

Introduction

Despite several impressive therapeutic advances in recent years, cancer remains the second-leading cause of death in the United States, and effective new therapies are still desperately needed. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory review is a complicated, expensive, and often inefficient process that can take up to 15 years. Included among the many challenges of drug development are the difficulties in recruiting cancer patients to clinical trials, the extensive bureaucratic processes required to initiate any clinical trial, and lengthy regulatory review. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.

FRIENDS of CANCER RESEARCH http://www.focr.org/events/design-lung-cancer-master-protocol

Major Elements

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- **Setting:** Squamous cell carcinoma (SCCA), advanced stage, 2nd line therapy

- **Agents:** Candidate drugs must demonstrate biologic activity against a measurable target with a proposed predictive biomarker

- **Study design:** Multi-arm randomized, controlled phase II/III master registration protocol. Each arm able to open and close independent of other arms

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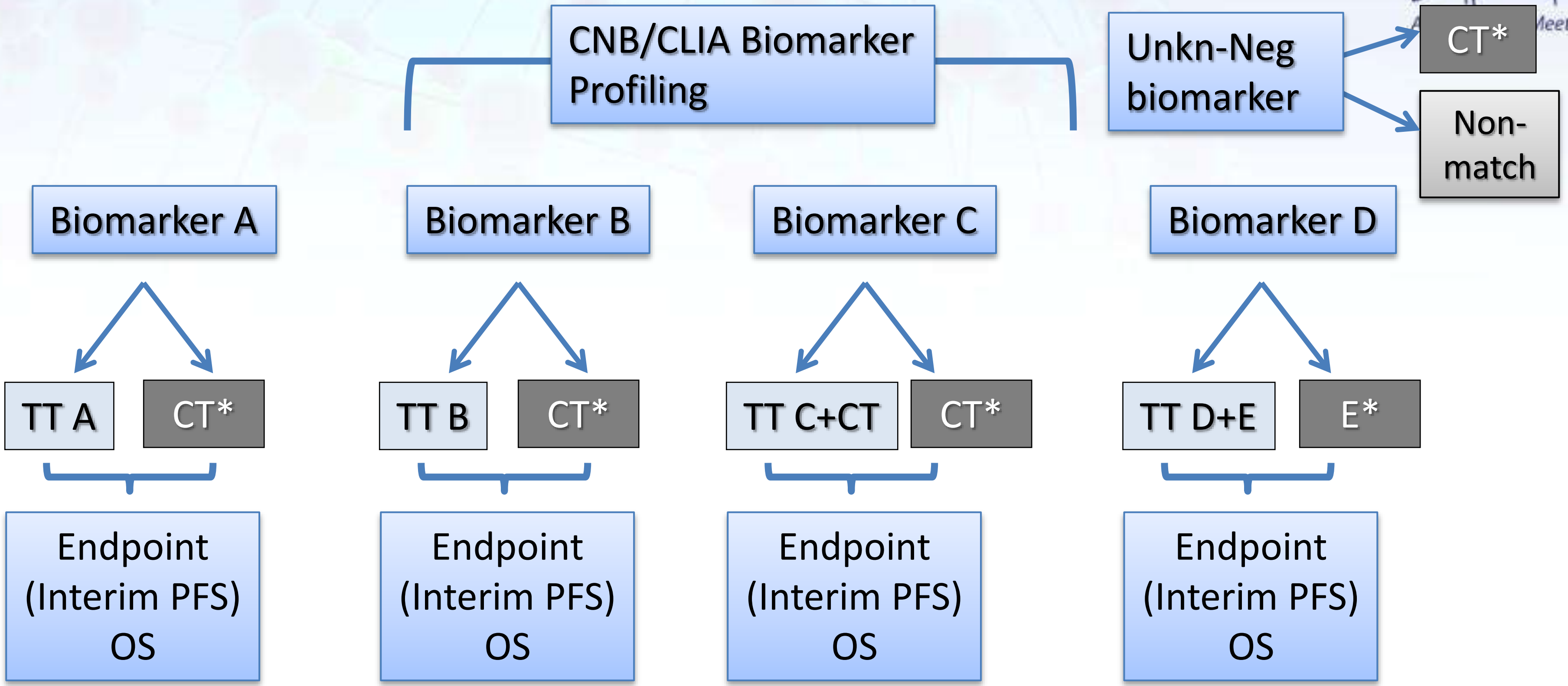
MASTER PROTOCOL

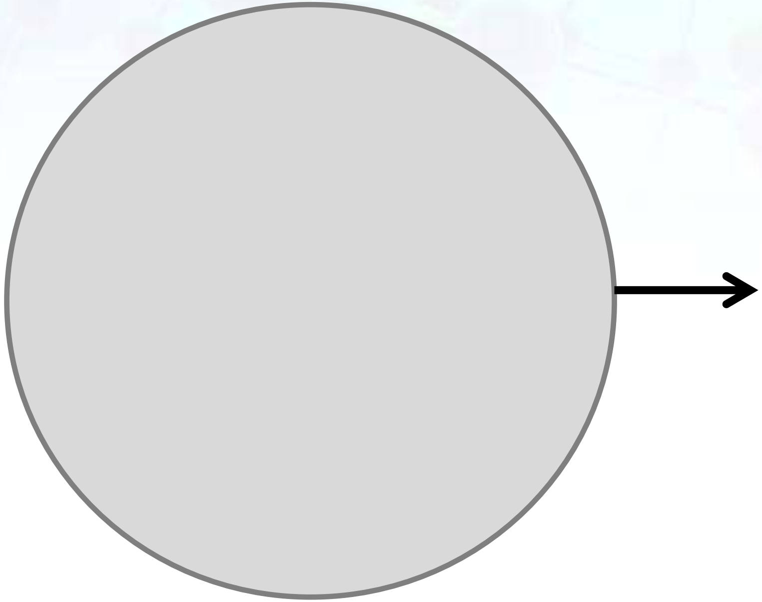


TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

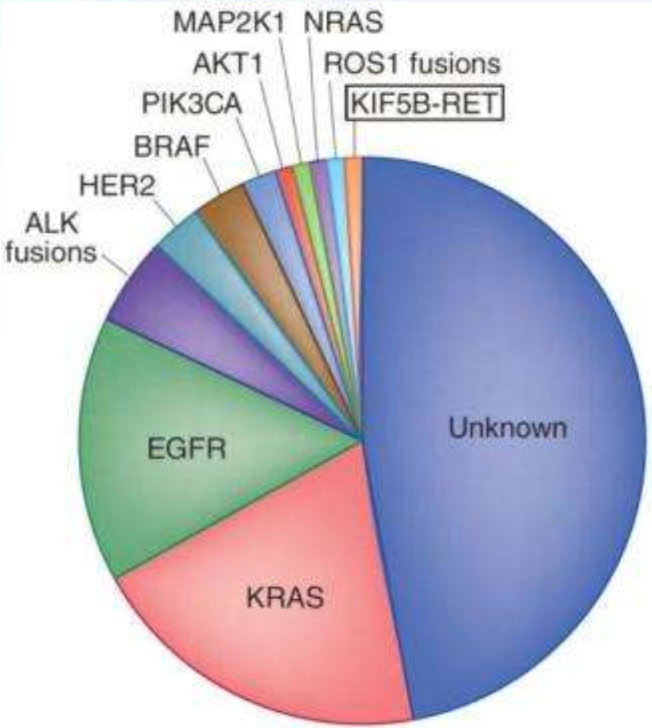
Courtesy of: Vali Papadimitrakopoulou

Lung Adenocarcinoma

2003



2012



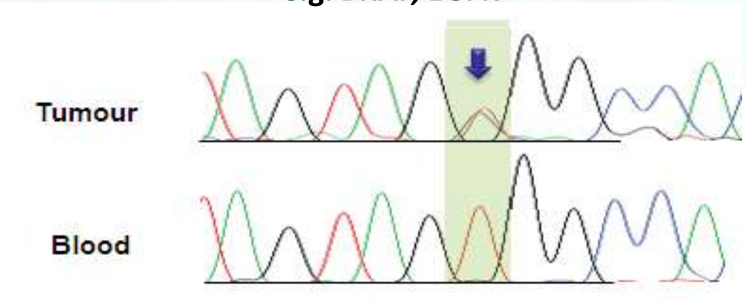
Matching the correct targeted therapy to the correct patient is diagnostically challenging as the number of "clinically relevant" genomic alterations increases

Pao and Hutchinson, Nature Medicine 2012. 18:349-351

Diagnostic challenge: There are multiple types of clinically relevant genomic alterations

Base Substitutions

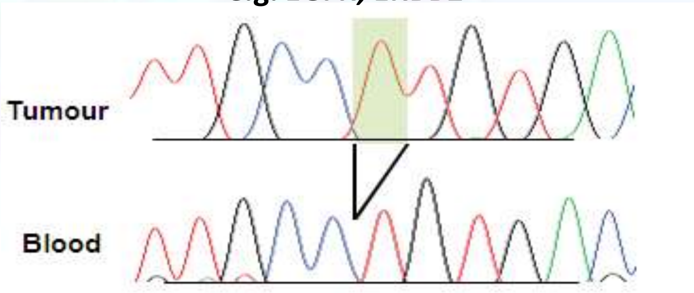
e.g. *BRAF, EGFR*



Capillary sequencing, Mass Spectrometry

Short Insertions/Deletions

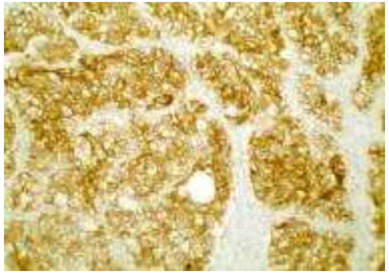
e.g. *EGFR, ERBB2*

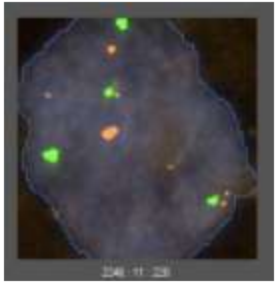


Capillary sequencing, gel size shift assays

Focal Amplification & Homozygous Deletion

e.g. *HER2, MET* e.g. *PTEN, TSC1/2*

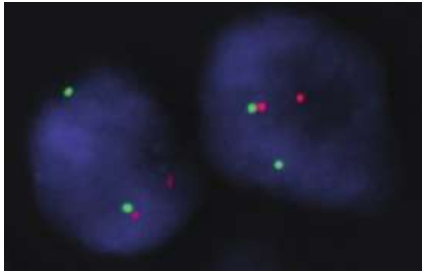




IHC (overexpression), Fluorescence *In Situ* Hybridization

Gene Fusion

e.g. *ALK, RET*

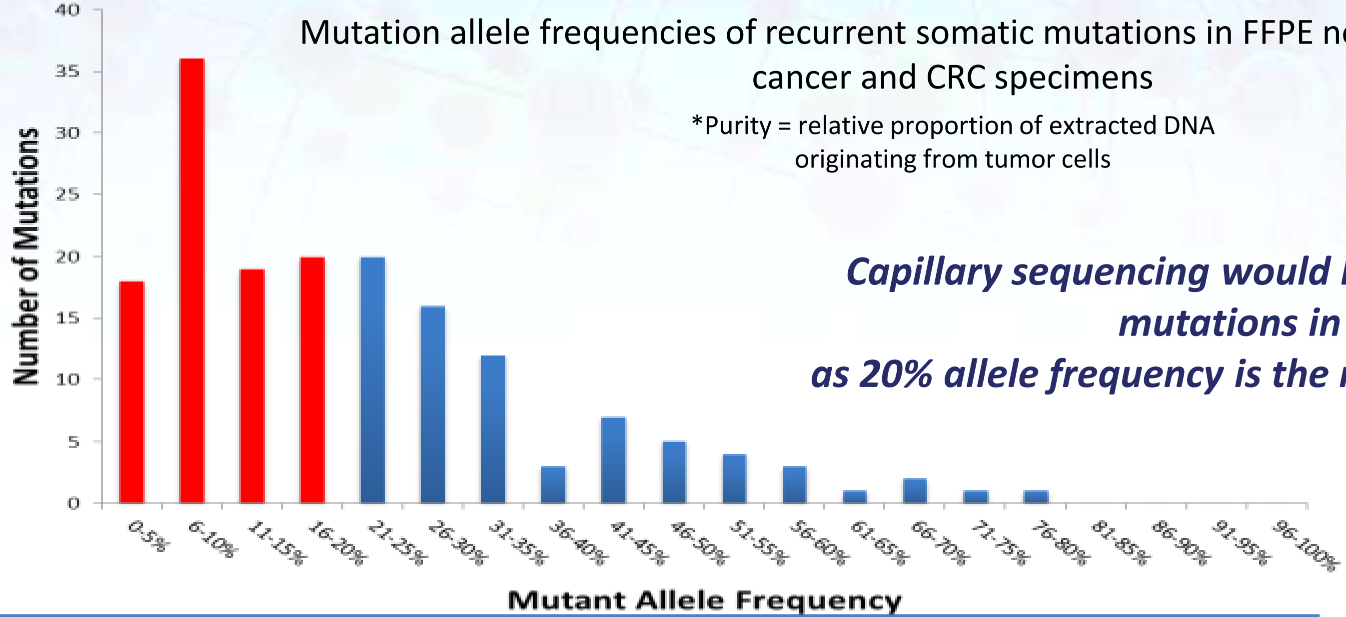


RT-PCR Fluorescence *In Situ* Hybridization

Diagnostic challenge: Low tumor purity in many clinical specimens requires tests with high accuracy

Mutation allele frequencies of recurrent somatic mutations in FFPE non-small cell lung cancer and CRC specimens

*Purity = relative proportion of extracted DNA originating from tumor cells

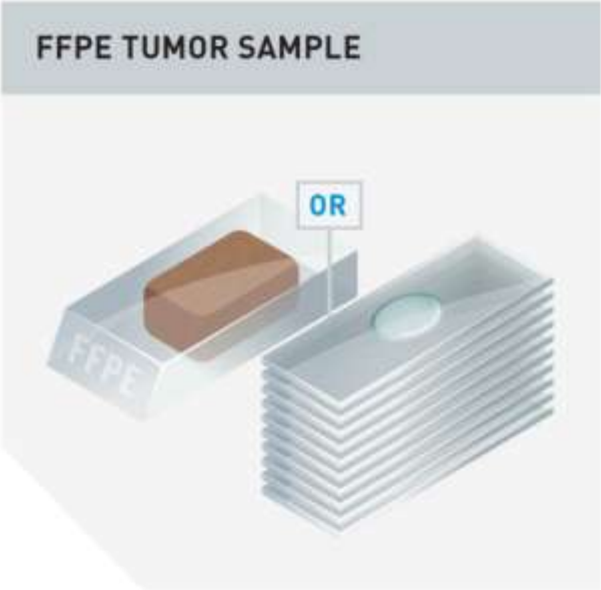


Capillary sequencing would have missed over half the mutations in this study as 20% allele frequency is the maximum limit of detection

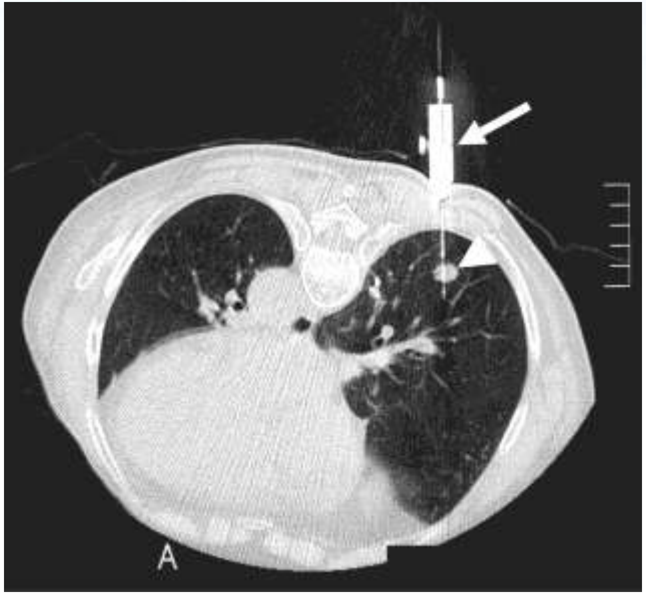
Fraction of mutations <5%	**Fraction of mutations <10%**	**Fraction of mutations <20%**	Fraction of mutations <25%	Fraction of mutations <50%	Fraction of mutations <100%
11%	**32%**	**55%**	67%	93%	100%

Diagnostic challenge: Many clinical cancer specimens are small FFPE processed needle biopsies, FNAs, etc.

Formalin fixation and subsequent storage can damage nucleic acids



Percutaneous needle biopsy of lung nodules under CT fluoroscopic guidance



Sample preparation needs be optimized to maximize accuracy and isolate sufficient material for diagnostic testing from tiny specimens

FoundationOne™: Comprehensive NGS-based genomic profiling assay specifications

- One comprehensive genomic profile for all solid tumors to simultaneously detect all clinically relevant classes of genomic alterations in a single assay
- Focused on 236 known clinically & biologically relevant cancer genes (all coding exons and selected introns)
- Validated high accuracy achieved by high, uniform coverage: >99.5% of exons covered >100X
- Requires small amounts of tissue routine FFPE samples including needle biopsies (≥50ng of DNA)
- Customized computational biology algorithms validated for high accuracy in clinical samples with high stromal contamination

FoundationOne™: Comprehensive NGS-based genomic profiling assay workflow (14-17 days)

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1) DNA/RNA extraction:
Extensive optimization

2) LC, Hybrid Capture:
Extensive optimization

3) Analysis pipeline:
Advanced computational biology

4) Clinical report:
Resource intensive

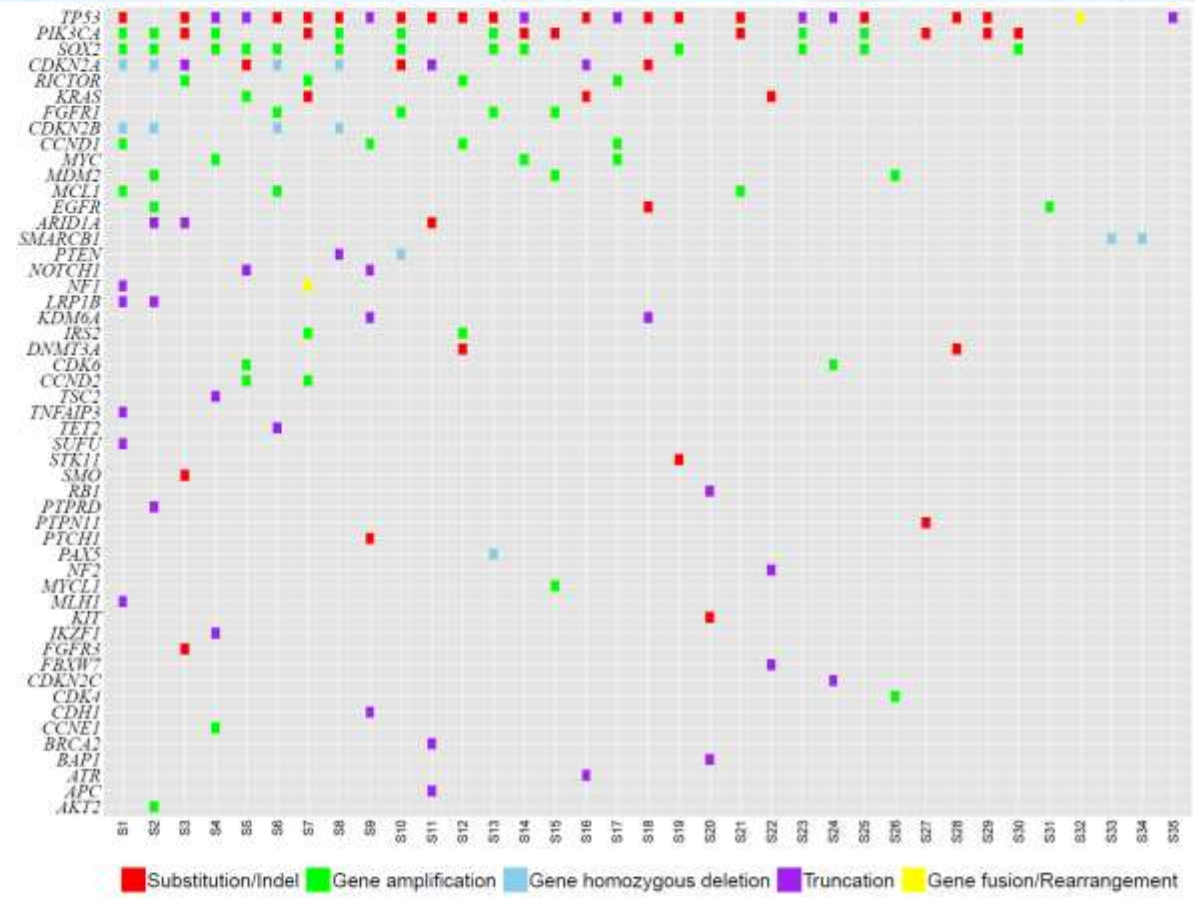
Illumina HiSeq

Pre-Analytic Process (Pre-Sequencing)

Post-Analytic Process (Post-Sequencing)

Translating research grade NGS to a clinical cancer diagnostic assay requires extensive optimization and investment

The Landscape of Genomic Alterations in Lung SCCa



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The Landscape of Genomic Alterations in Lung SCCa

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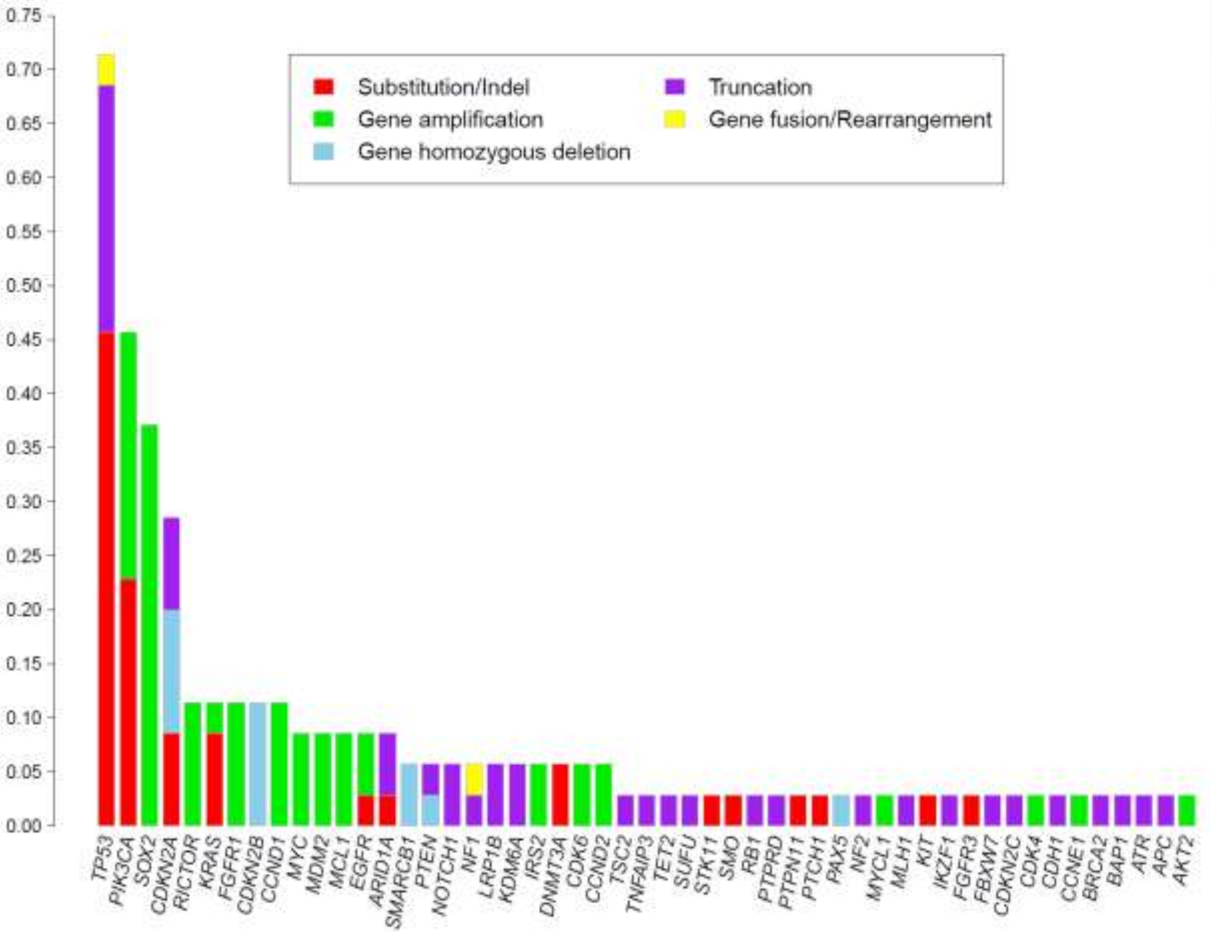
% of patients



Genomic Biomarkers Observed in Lung SCCa Relevant to Therapies Under Development

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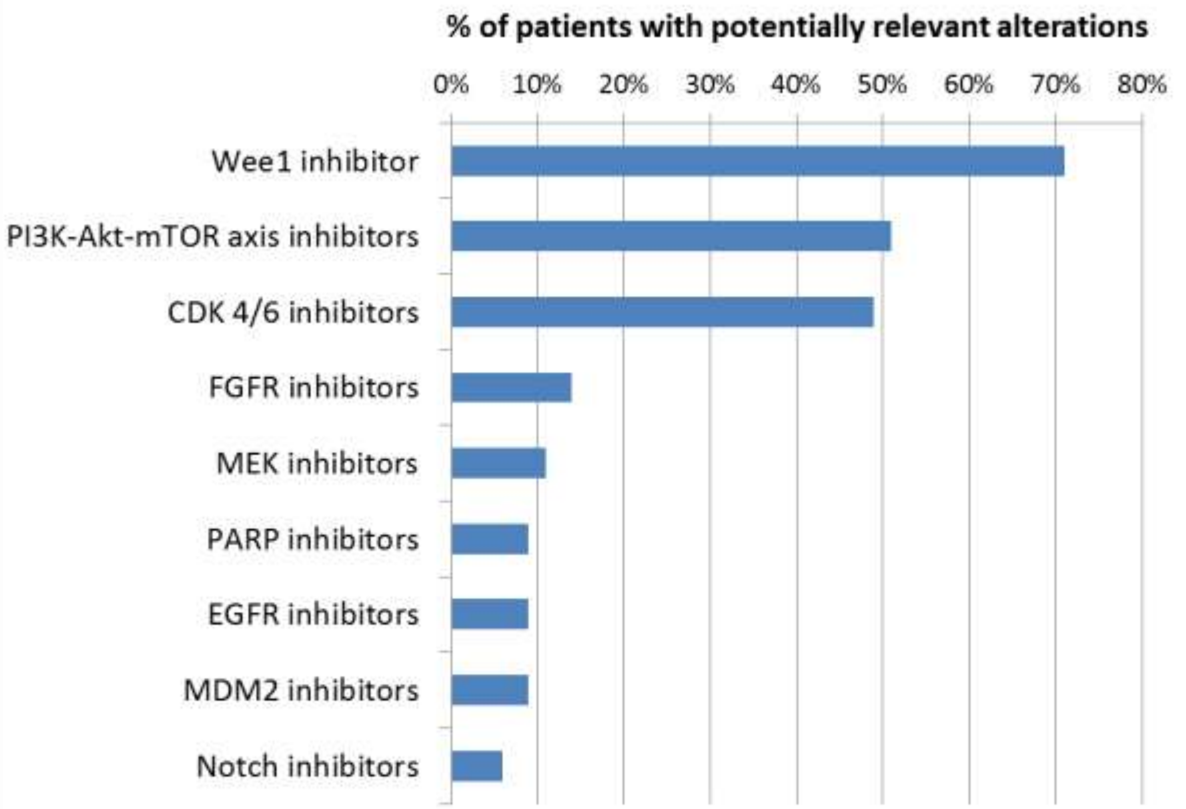

TP53 (0.71)					
PIK3CA (0.46)	PTEN (0.06)	AKT2 (0.03)	FBXW7 (0.03)	STK11 (0.03)	TSC2 (0.03)
CDKN2A (0.29)	CCND1 (0.11)	CCND2 (0.06)	CDK6 (0.06)	CCNE1 (0.03)	CDK4 (0.03)
FGFR1 (0.11)	FGFR3 (0.03)				
KRAS (0.11)					
ATR (0.03)	BAP1 (0.03)	BRCA2 (0.03)			
EGFR (0.09)					
MDM2 (0.09)					
NOTCH1 (0.06)					

Study Design Within Each Biomarker-defined Subgroup

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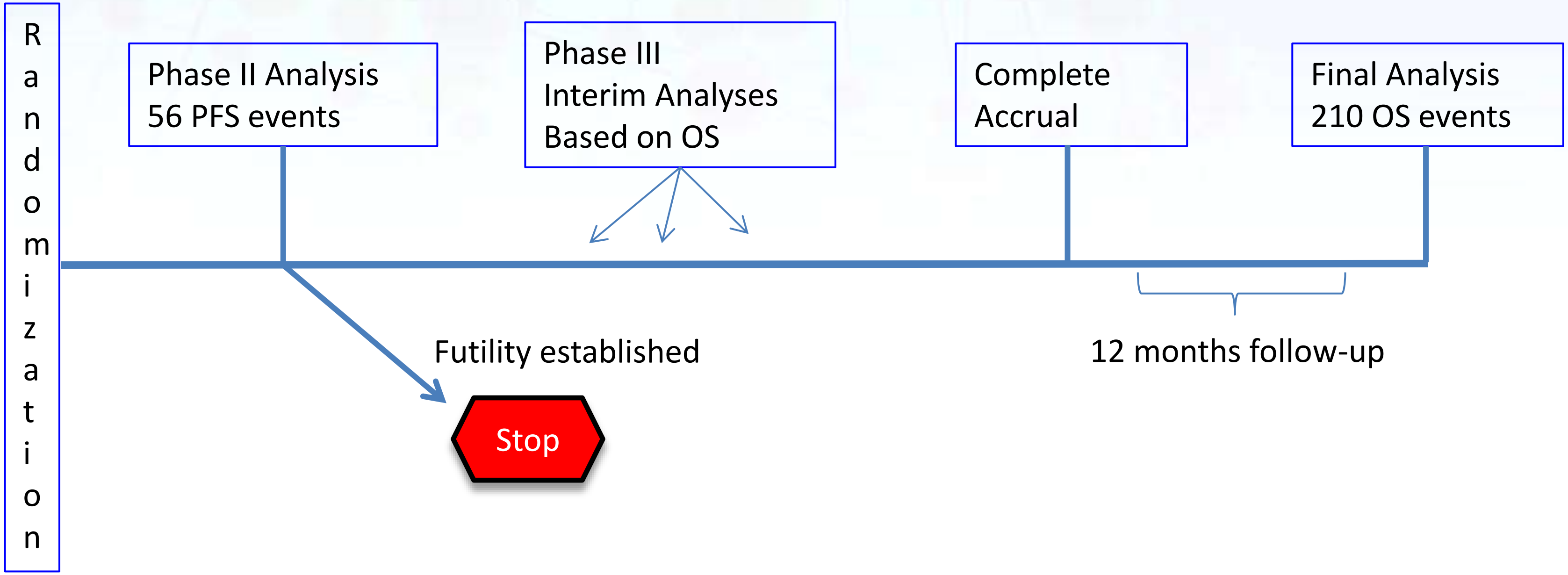

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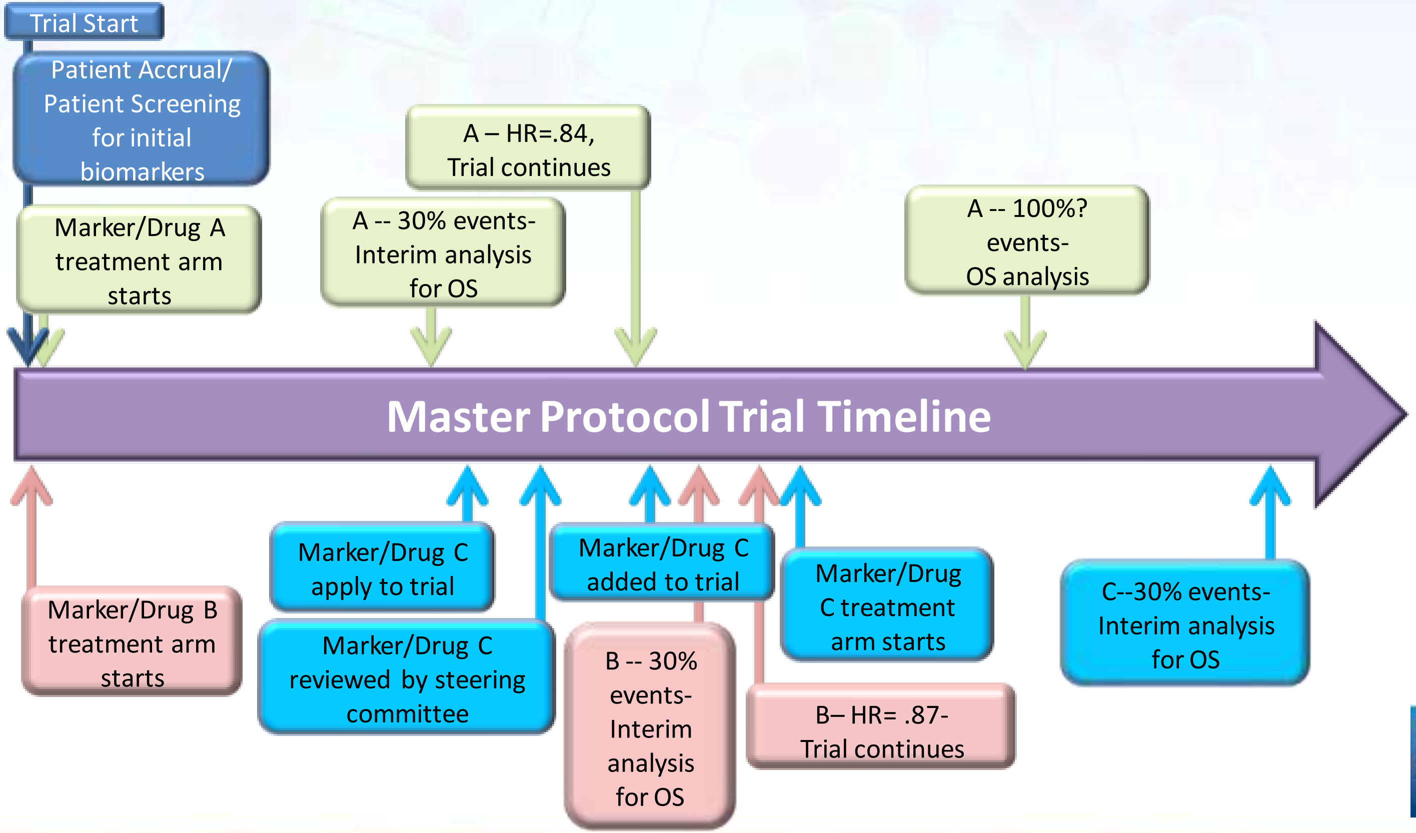
Courtesy of: Mary Redman

Master Protocol over time

Additional drug/biomarker combinations dropped and added to study



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Benefits of a Master Protocol

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- **Enrollment Efficiency:** Grouping these studies under a single trial reduces the overall screen failure rate
- **Operational Efficiency:** single master protocol can be amended as needed as drugs enter and exit the study
- **Consistency:** every drug entered into the trial would be tested in the identical manner
- **Predictability:** If pre-specified efficacy and safety criteria are met, the drug and accompanying companion diagnostic will be approved
- **Patient Benefit:** offers the advantage of bringing safe and effective drugs to patients sooner than they might otherwise be available.

Expert Working Group

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- Roy Herbst – Yale University
- David Gandara – UC Davis
- Ellen Sigal – Friends of Cancer Research
- Vali Papadimitrakopoulou – MD Anderson
- Fred Hirsch – University of Colorado
- Mary Redman - Fred Hutchinson Cancer Center
- Jeff Abrams – National Cancer Institute
- Jack Welch – National Cancer Institute
- Shakun Malik – Food and Drug Administration
- David Wholley – Foundation for the NIH
- Eric Rubin – Merck
- Richard Gaynor – Eli Lilly
- David Chang - Amgen

Progress and Future Announcements

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***Friends of Cancer Research* –Brookings Institution Conference on Clinical Cancer Research**

November 7, 2013 –Washington, DC

- Public announcement of this innovative trial- Final details of the protocol will be presented.

- Drug selection to be announced Nov/Dec 2013

- Target date for initial accrual in early 2014.

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