ESMO Asia 20 Dec 2015
Developmental Therapeutics, Education session

The role of basket and umbrella protocols in drug development

Dr Daniel SW Tan
Consultant, Division of Medical Oncology
National Cancer Centre Singapore

Disclosures

- Advisory Role and Consultant: Novartis, Bayer, Boehringer Ingelheim
- Research Funding: Novartis

Background

- **Organ-based classification represents a heterogeneous group of molecular entities**
  - Vary in number of driver alterations
  - “Druggability”

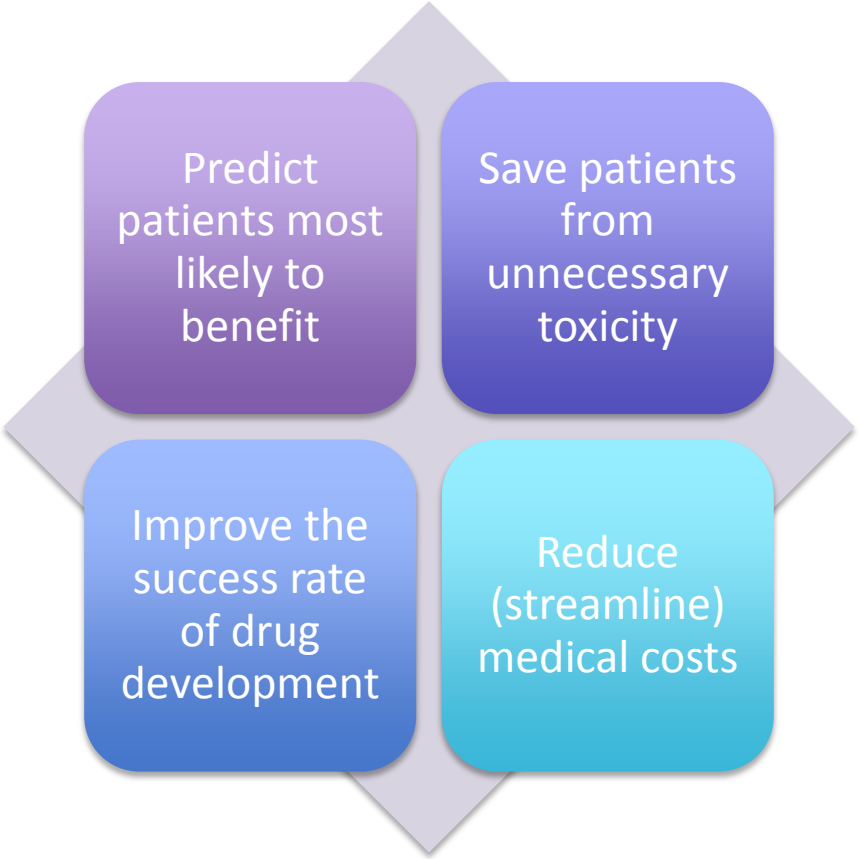
- **Many cancer treatments only work in a subset of cancers within these traditional disease classifications**
  - Particularly true for targeted therapies

- **Biomarker-directed therapies are the new reality**

Overview

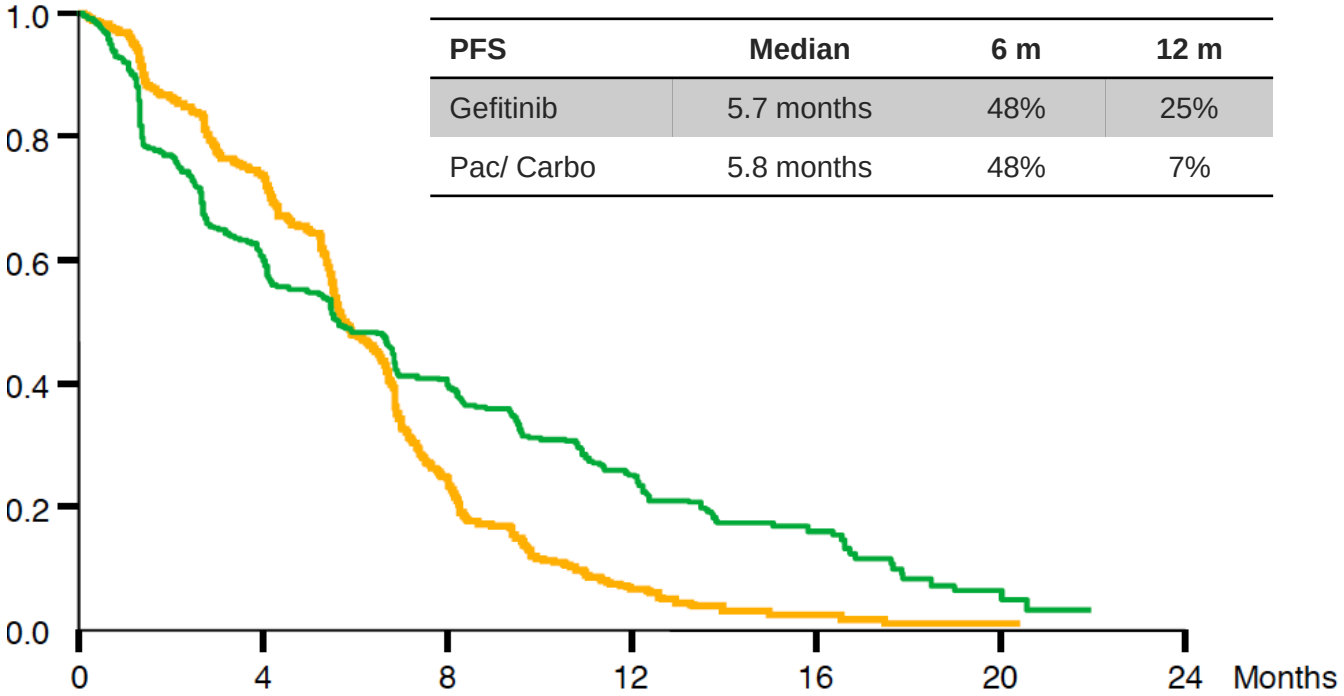
- **Biomarkers**
  - Classification: selection and intermediate endpoints
  - Performance
  - Precision
- **Prospective trial designs involving biomarkers**
- **Master protocols**
  - Basket and umbrella trials

Why biomarker-directed therapies?



i-PASS

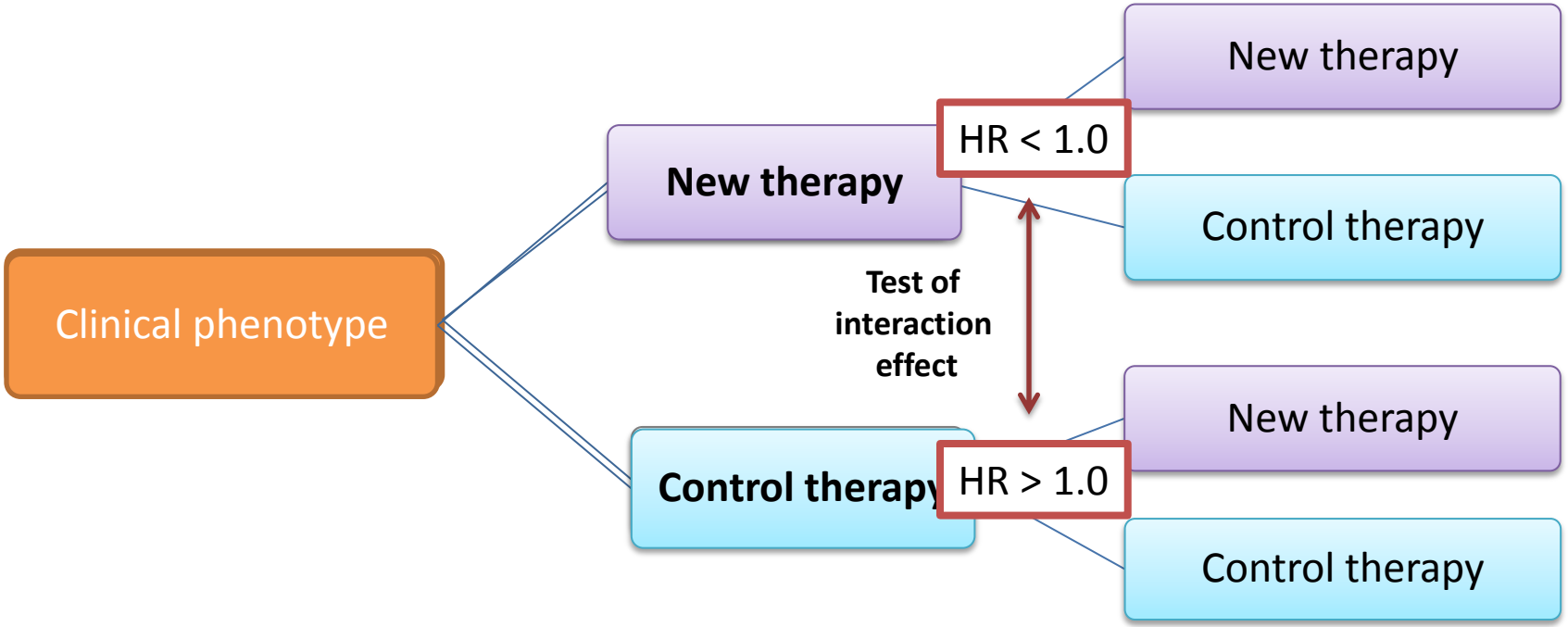
Light or Never-Smoker/ Asian/ Adenocarcinoma



PFS	Median	6 m	12 m
Gefitinib	5.7 months	48%	25%
Pac/ Carbo	5.8 months	48%	7%

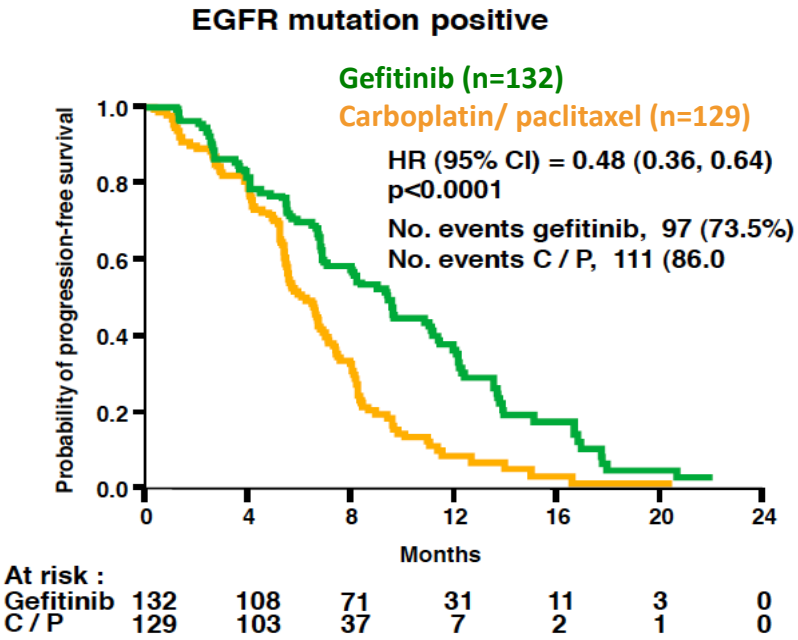
Mok et al. *NEJM* 2009

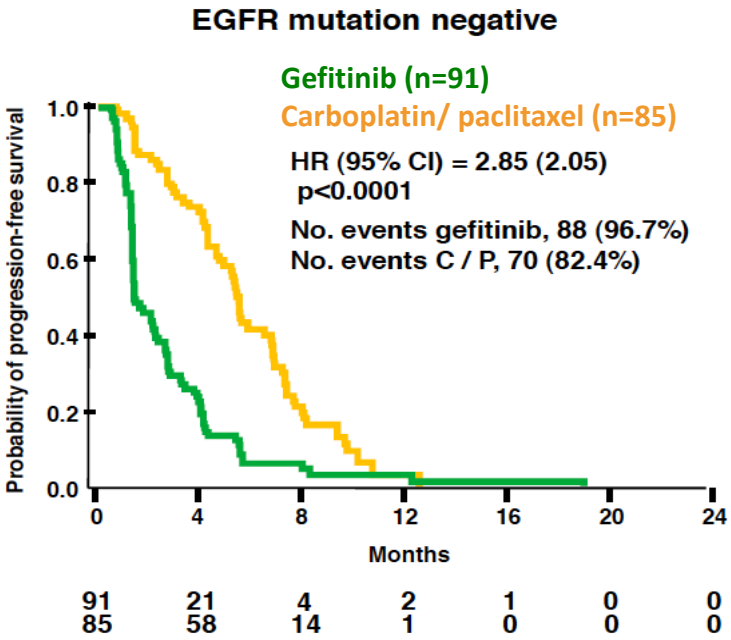
Clinical phenotype enrichment strategy



i-PASS

According to EGFR mutation status





Objective RR 71.2%

Objective RR 1.1%

Treatment by subgroup interaction test, p<0.0001

Mok et al. *NEJM* 2009

Prospective trial design considerations: Role of biomarker

- **All-comers with biomarker stratification**:
  - Consider results combined and separately within biomarker-positive and -negative subgroups

- **Biomarker enrichment**:
  - Biomarker positivity required for eligibility

- **Biomarker adaptive**:
  - Trial design features adapted during course of the trial depending on early results within biomarker-positive and negative subgroups

What are biomarkers?

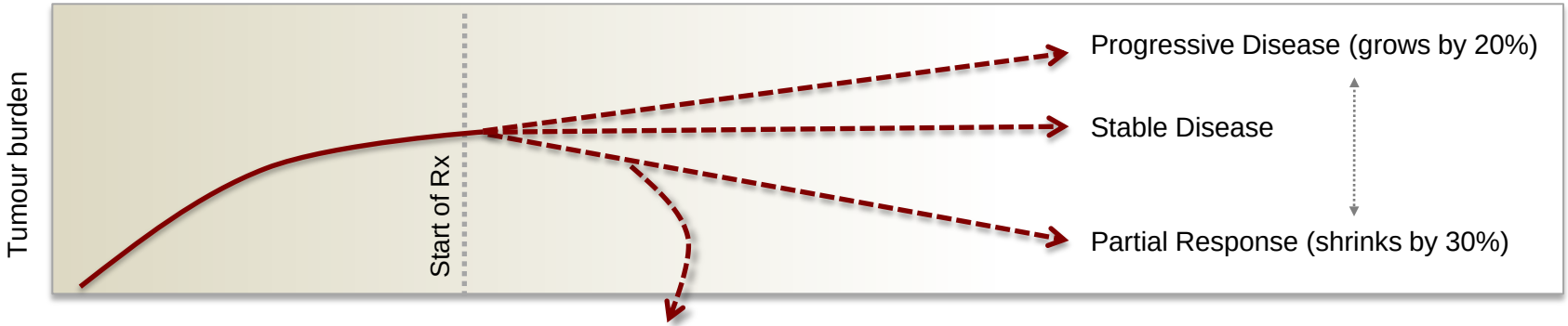
- **Biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention

Biomarkers Definitions Working Group
Clinical Pharmacology & Therapeutics (2001)
Vol 69, No 3, pp 89 - 95

Examples

- CT imaging
- Serum tumour markers e.g. PSA in prostate cancer
- ER/ PR/ HER-2 status in breast cancer
- *EGFR* mutations & *ALK* translocations in lung cancer

Biomarker-driven clinical trials



PROGNOSTIC

HER2 amplification
KRAS/ BRAF mutations

PREDICTIVE

HER-2 amplification
EGFR exon 19 del
PTEN loss
PIK3CA mutations
MET amplification
PDL1 expression

Improved Patient Selection

PHARMACODYNAMIC

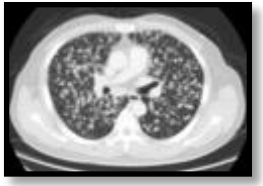
Tissue Based
Target modulation
Histopathologic changes

Minimally invasive
Circulating DNA/ CTC
Other biospecimens e.g. sputum

Imaging based
Hypoxia imaging

Better Intermediate Activity Readouts

RADIOGRAPHIC CHANGES



RECIST 1.1

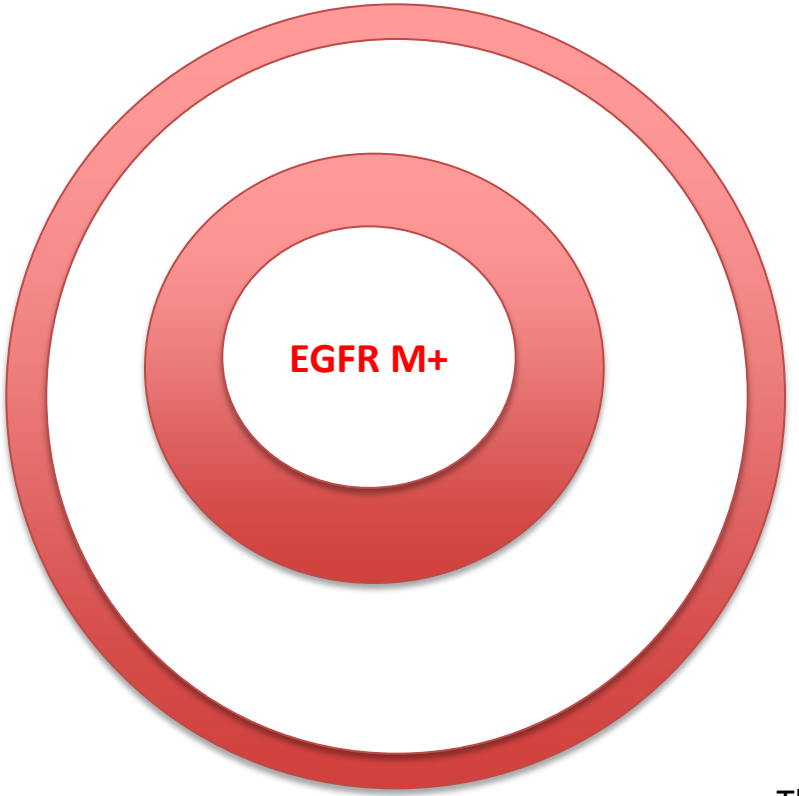
BIOLOGICAL PROGRESSION MARKERS

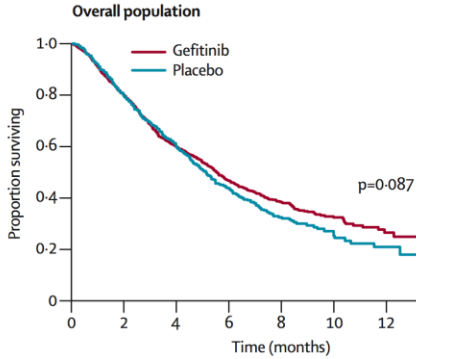
- Tumour markers e.g. PSA, CA-125

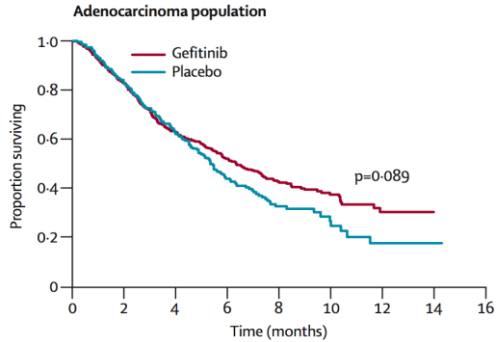
Response Evaluation

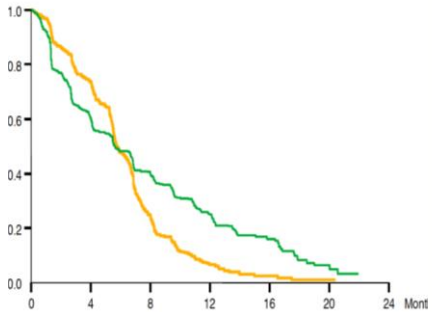
Influence of biomarker on trial outcomes

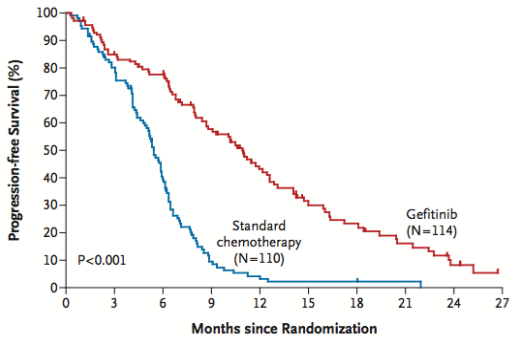
EGFR TKI as an example





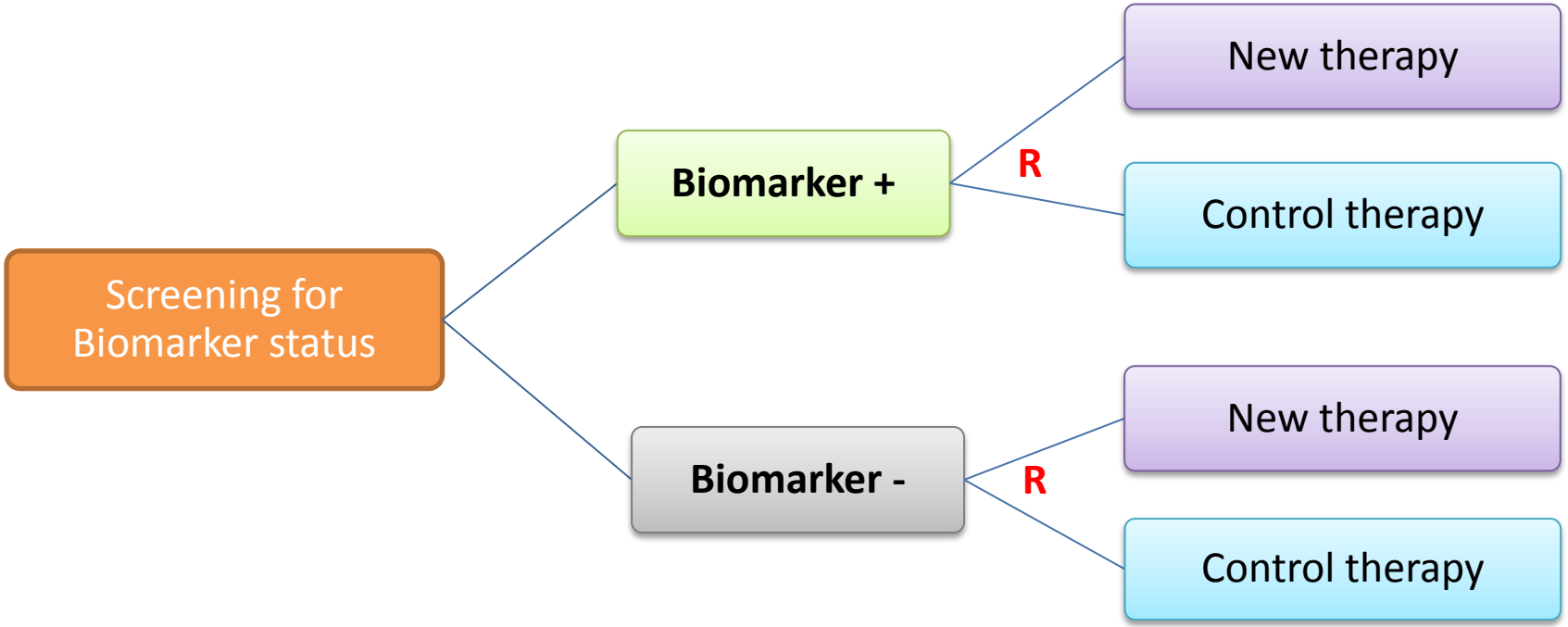






Thatcher Lancet 2005, Mok et al. NEJM 2009, Maemondo NEJM 2010

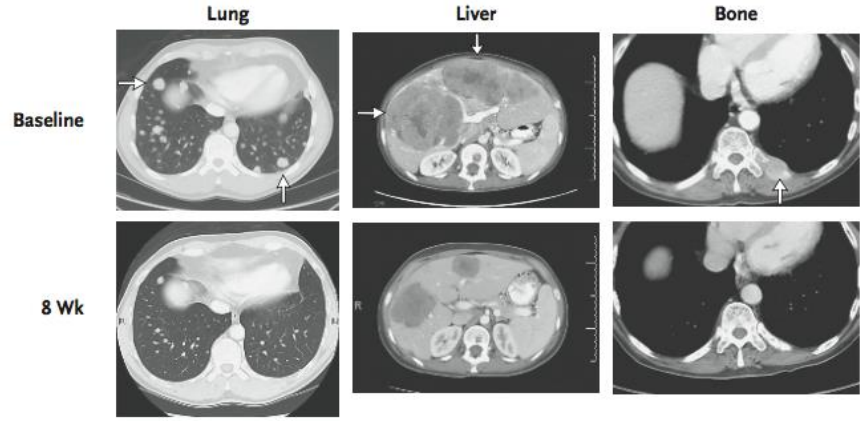
Randomized biomarker-stratified designs

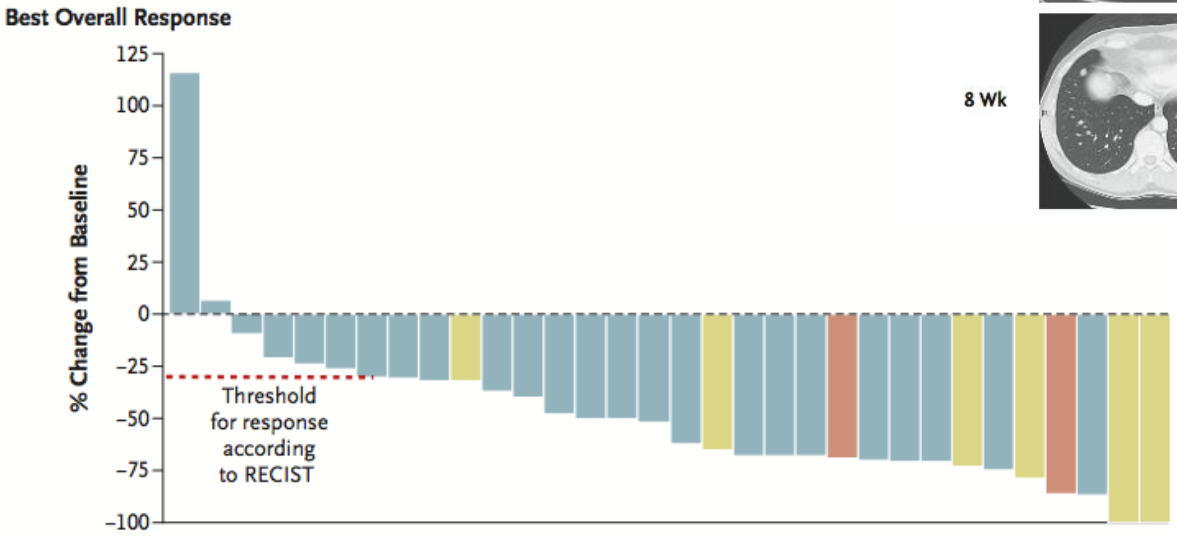


This design maximizes information and controls for the prognostic effect of the marker, **but**…

Phase I trial of PLX4032

Dose escalation: 11 out of 16 responded (69%)
Dose expansion: 26 out of 32 responded (81%)





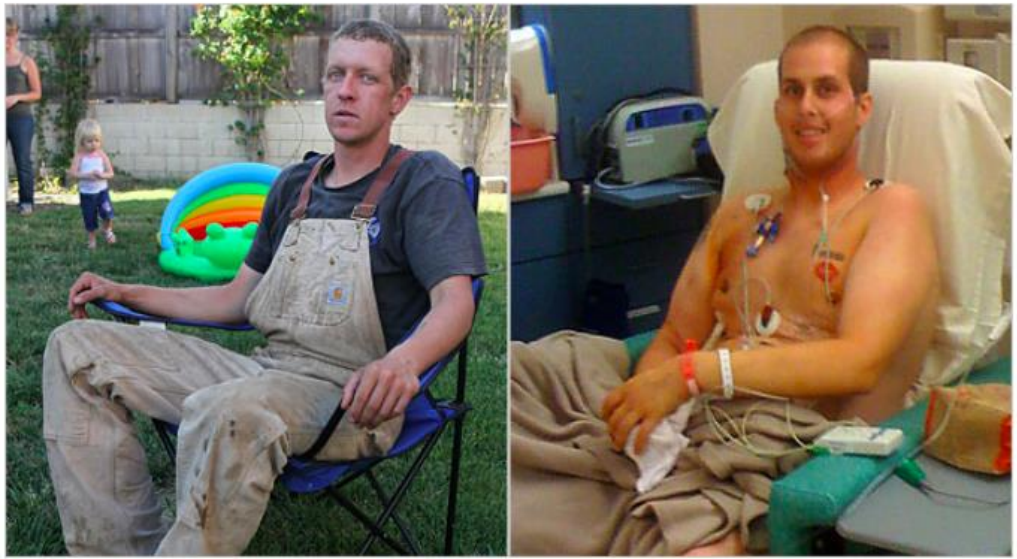
Flaherty et al. NEJM 2010

Can a phase III trial not have crossover?

RESEARCH | TARGET CANCER

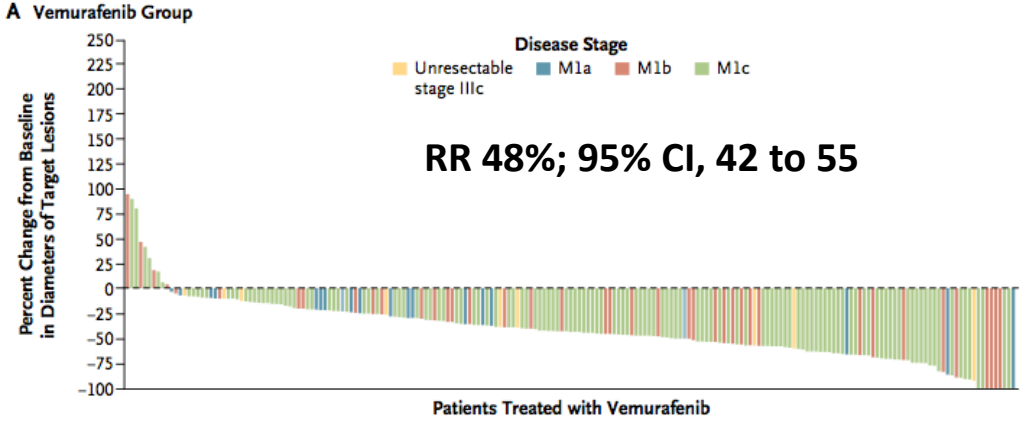
New Drugs Stir Debate on Rules of Clinical Trials

By **AMY HARMON** SEPT. 18, 2010

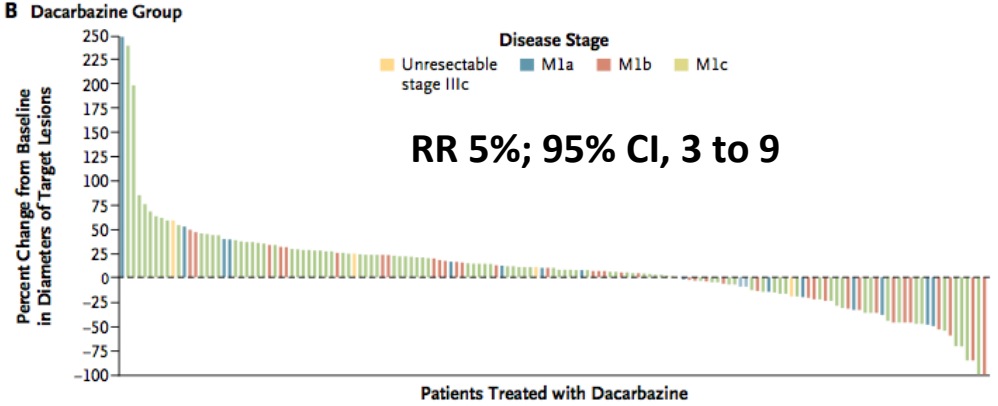


Two Cousins, Two Paths Thomas McLaughlin, left, was given a promising experimental drug to treat his lethal skin cancer in a medical trial; Brandon Ryan had to go without it. Monica Almeida/The New York Times, left

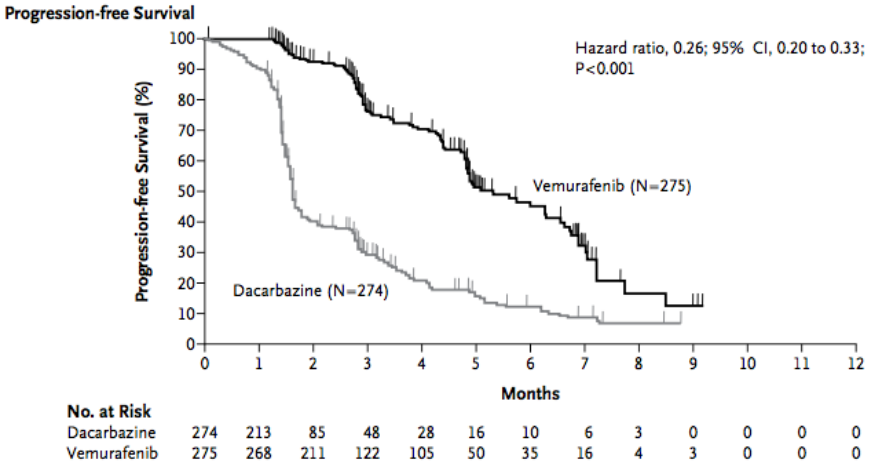
Vemurafenib in *BRAF*^{V600E} cutaneous melanoma



RR 48%; 95% CI, 42 to 55



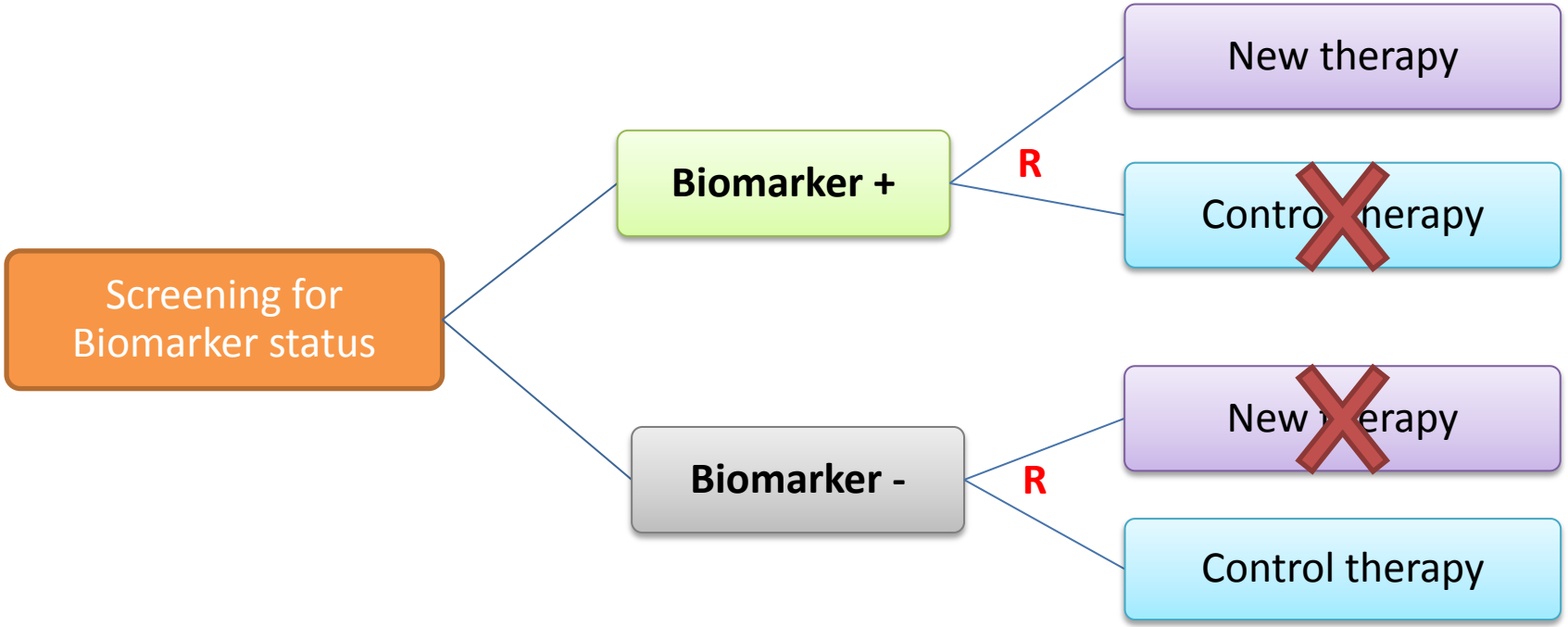
RR 5%; 95% CI, 3 to 9



5.3 vs 1.6 months

Chapman et al. NEJM 2011

Randomized biomarker-stratified designs



Difficult to justify the "control" arms in this era of high precision drugs and biomarkers

Prospective Trial Design Considerations: Role of Biomarker

- **All-comers with biomarker stratification**:
  - Consider results combined and separately within biomarker-positive and -negative subgroups

- **Biomarker enrichment**:
  - Biomarker positivity required for eligibility

- **Biomarker adaptive**:
  - Trial design features adapted during course of the trial depending on early results within biomarker-positive and negative subgroups

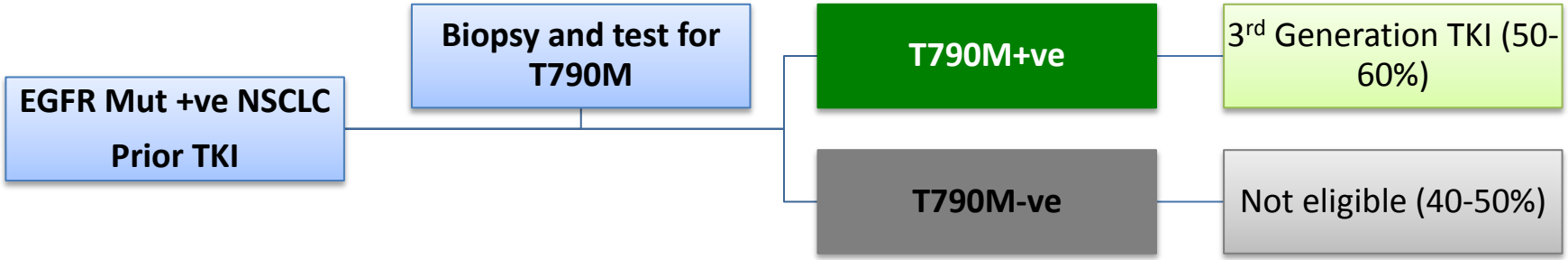
Biomarker-enrichment trial designs

- **Rationale**
  - Individual variation influences a treatment randomly, we can control for this through replication
  - But, when anticipated effect in a selected group is high, then we need to identify patients

- **Performance and precision of biomarker is a critical consideration**
  - Impact on sample size requirements (prevalence)
    - Screening strategy
    - Feasibility
  - Demonstration of desired effect (efficacy boundaries)

An example of biomarker enrichment: T790M

High biomarker prevalence (50-60%)



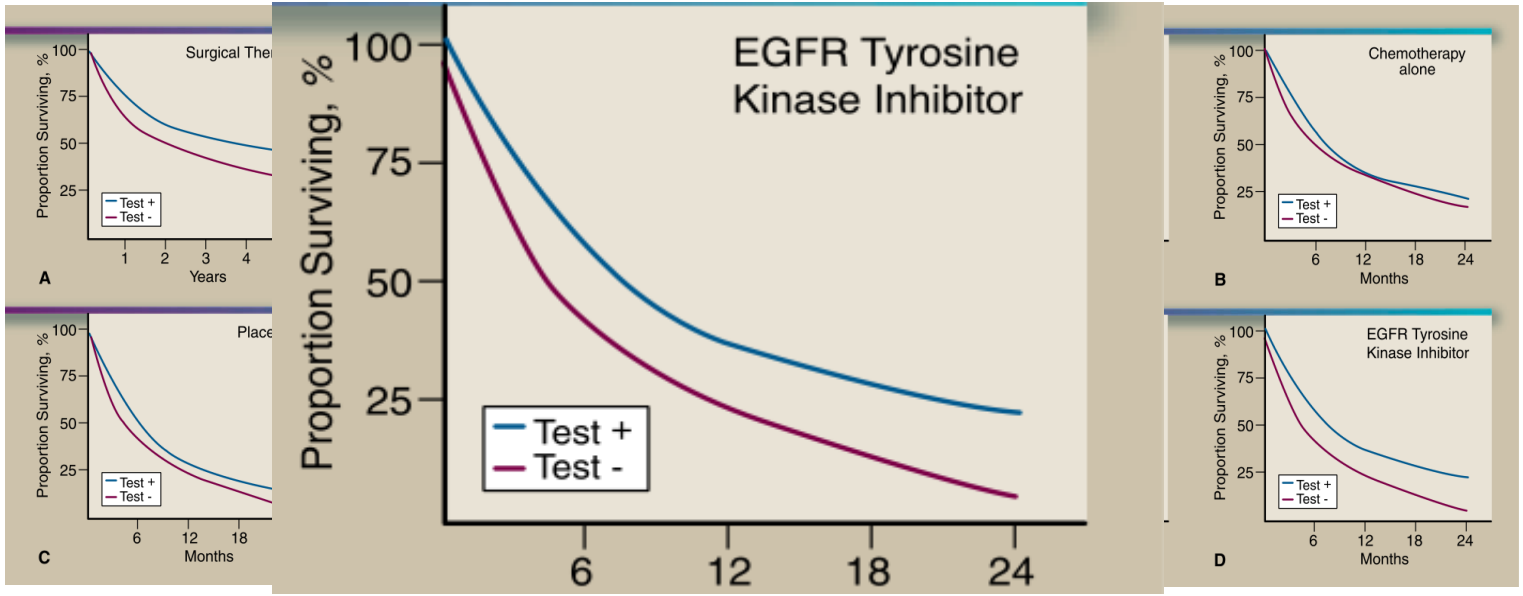
- Strong biologic rationale
- Marker-negative patients are unlikely to benefit

Caveats in interpreting predictive biomarker

- Prognostic or predictive
- Biological heterogeneity
- Performance of biomarker
- Precision of biomarkers

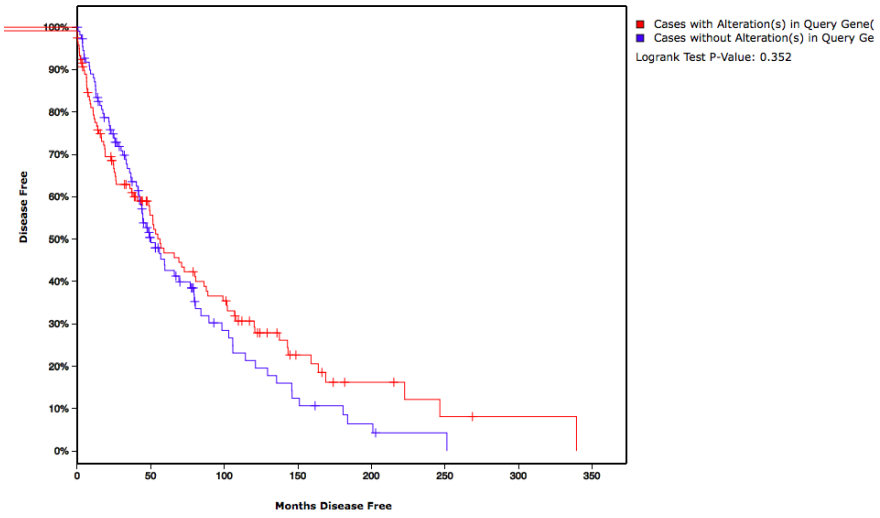
Is biomarker prognostic or predictive?

- **Tumour shrinkage (RECIST responses) are re-assuring**
- **Prolonged stable disease**
  - is this patient selection or true therapeutic effect?



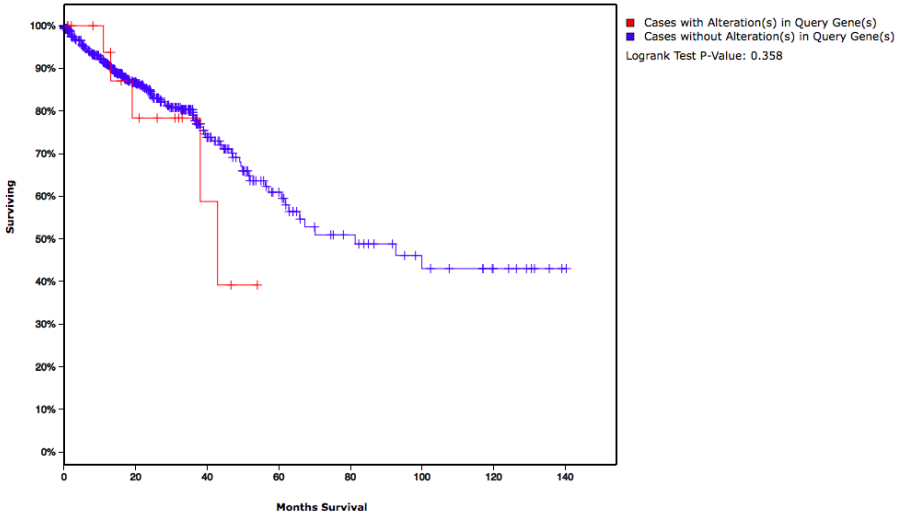
Prognostic impact of BRAF mutations (red curve)

Cutaneous Melanoma



	#total cases	#cases relapsed	median months disease free
Cases with Alteration(s) in Query Gene(s)	119	82	56.34
Cases without Alteration(s) in Query Gene(s)	111	79	50.13

Colorectal Cancer



	#total cases	#cases deceased	median months survival
Cases with Alteration(s) in Query Gene(s)	22	5	42.87
Cases without Alteration(s) in Query Gene(s)	586	106	81.31

cBioPortal for Cancer Genomics

Performance of a biomarker

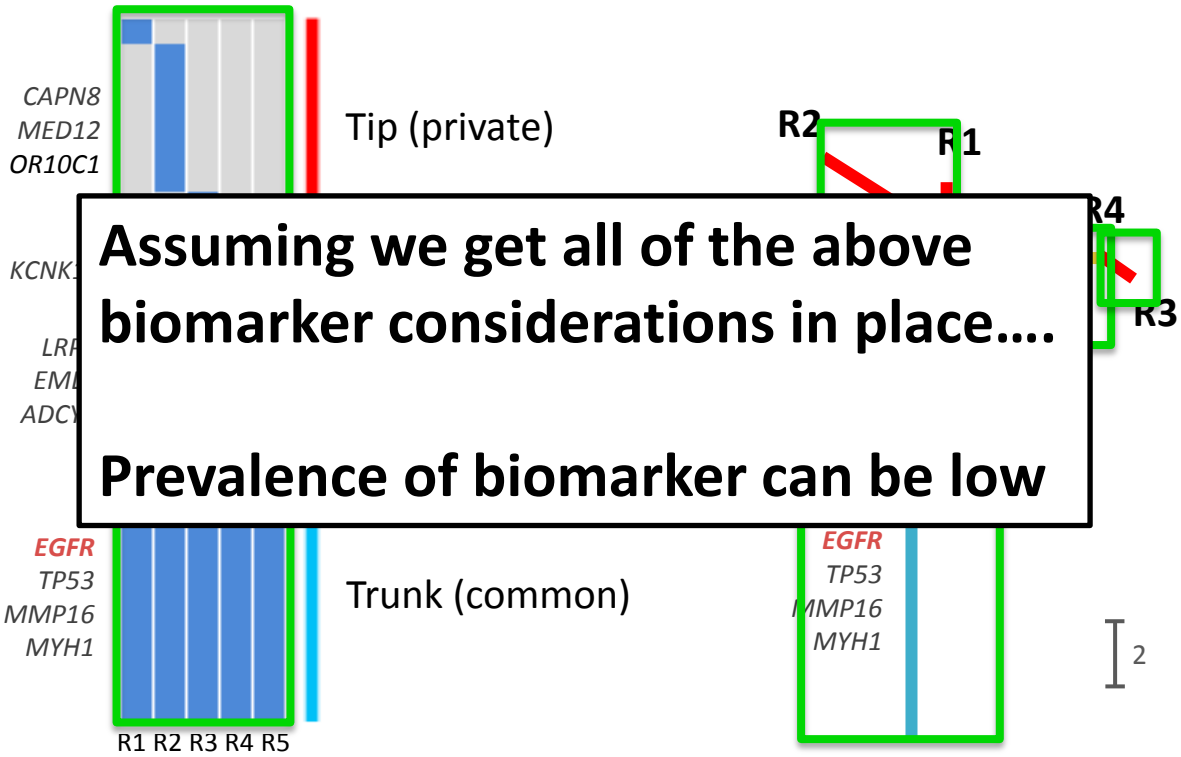
Key considerations

Fit-For-Purpose	• Extent of validation depends on decision making role within trial • Exploration-Demonstration-Characterization-Surrogacy
Validation	• Pre-analytical considerations • Scientific: preclinical modeling e.g. predictive animal models • Technical: reproducibility, dynamic analytic range
Qualification	• Pre-analytical considerations • Clinical qualification: correlation of exposure with outcome • GLP/ CLIA certified labs
Commercialization	• Technical standardization across all sites (Scalability) • Companion diagnostics

Tan et al. Cancer J 2009

Biological heterogeneity

ascertaining clonal vs subclonal drivers



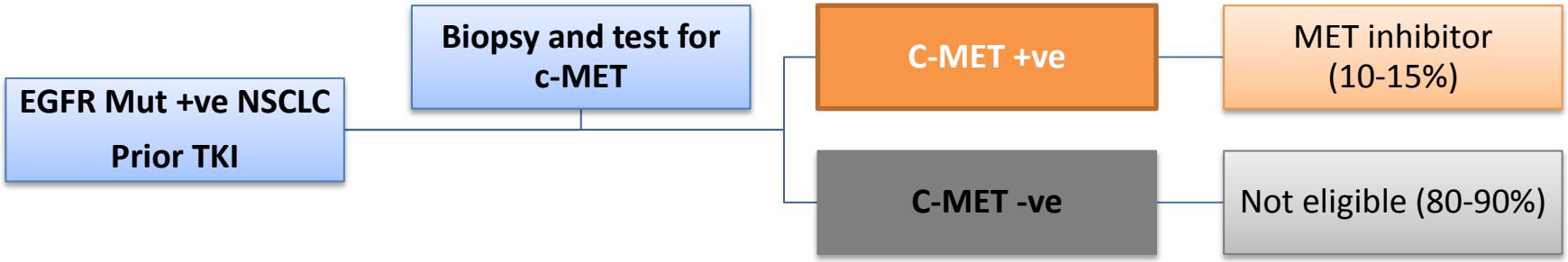
Assuming we get all of the above biomarker considerations in place….

Prevalence of biomarker can be low

Tan et al. WCLC 2015

Biomarker enrichment

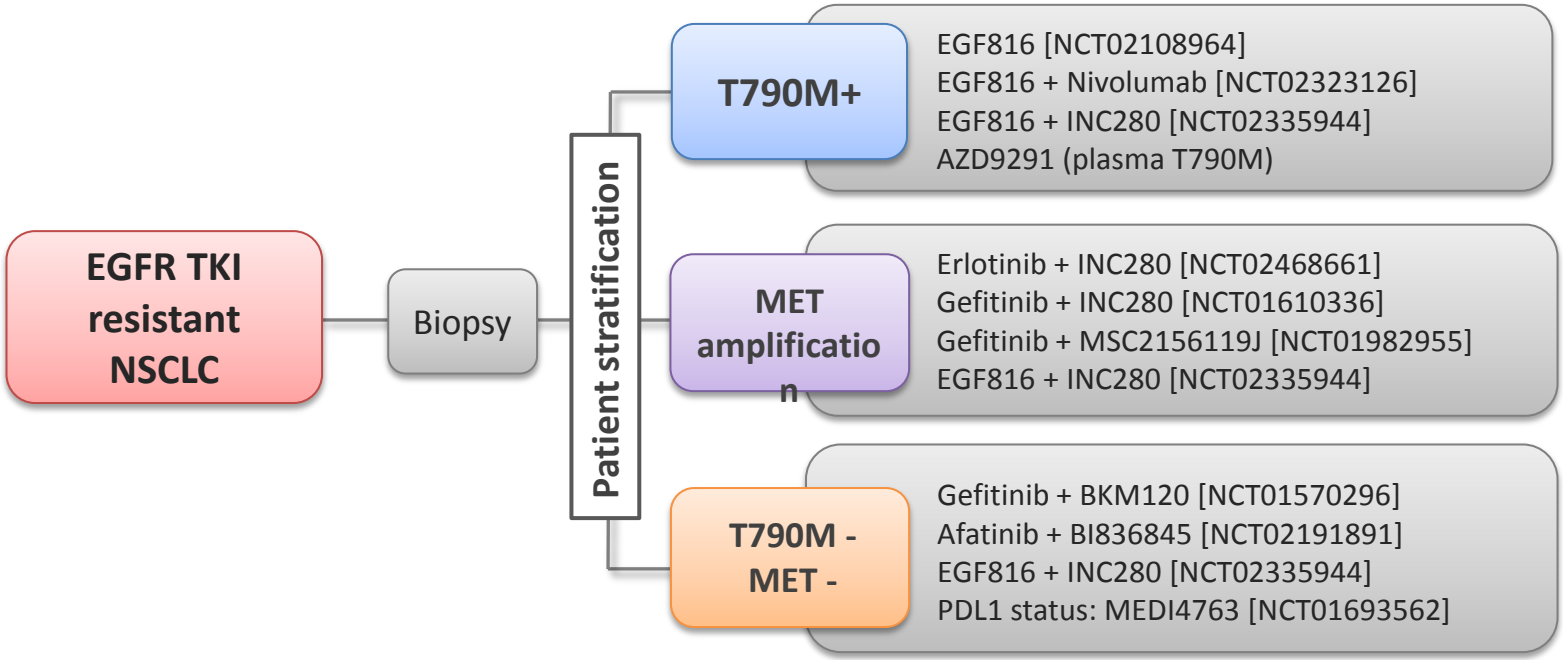
Low biomarker prevalence (10-15%)



- Large number of patients to be screened
- Likelihood of not being eligible is very high
- No option for screen negative patients
- Low enthusiasm among patients and providers

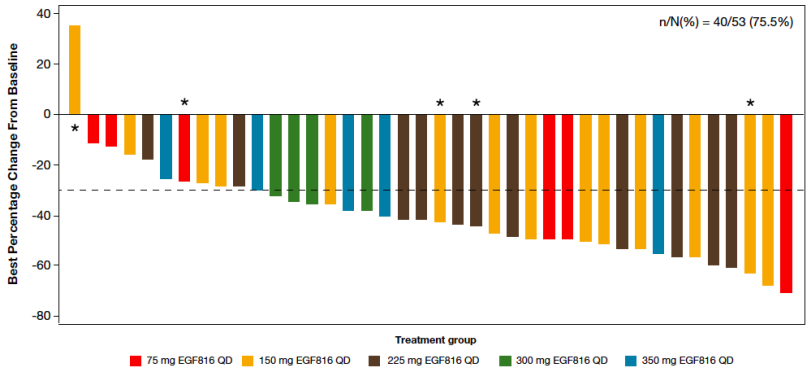
Clinical trials currently available targeting EGFR TKI resistance

Experimental Cancer Therapeutics Unit, NCCS



Biomarker precision

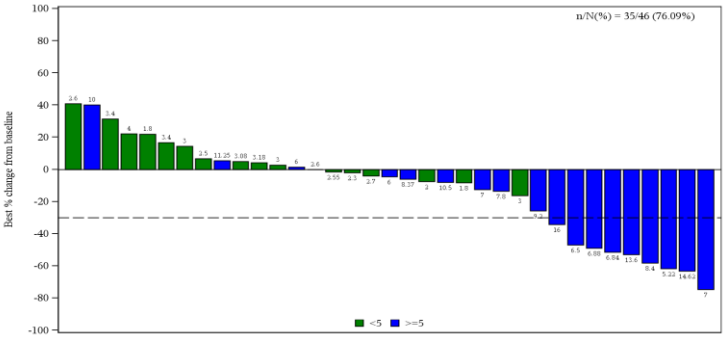
T790M (3rd generation EGFR TKI)



- **T790M positive vs negative**
  - Sequencing/ NGS

Tan DS ASCO 2015

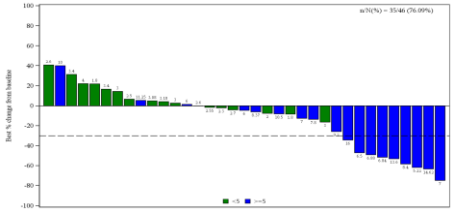
MET amplification >/= 6 copies (Gef-INC280)



- **“MET activated”**
  - IHC expression
  - C-MET FISH (cutoff)
  - Exon 14 skipping mutations

Wu YL, Tan DS ASCO 2014

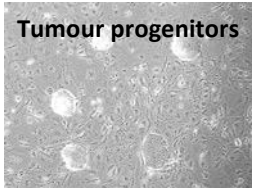
Biomarker and drug development is an iterative process

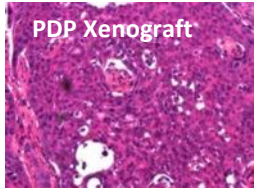


Clinical experience

Identify & Refine

Biomarker development ⟷ **Preclinical insights**





Patient-derived progenitor and PDX models

Model response/ resistance mechanisms

How do we accelerate drug and biomarker development?

- **Resources for pre-clinical work and assay development**

- **Broadly accessible trials to accrue sufficient numbers in small biomarker subgroups**
  - Multi-arm master protocol trials (“basket”, “umbrella” trials) give options for more patients/ fewer biomarker-negative

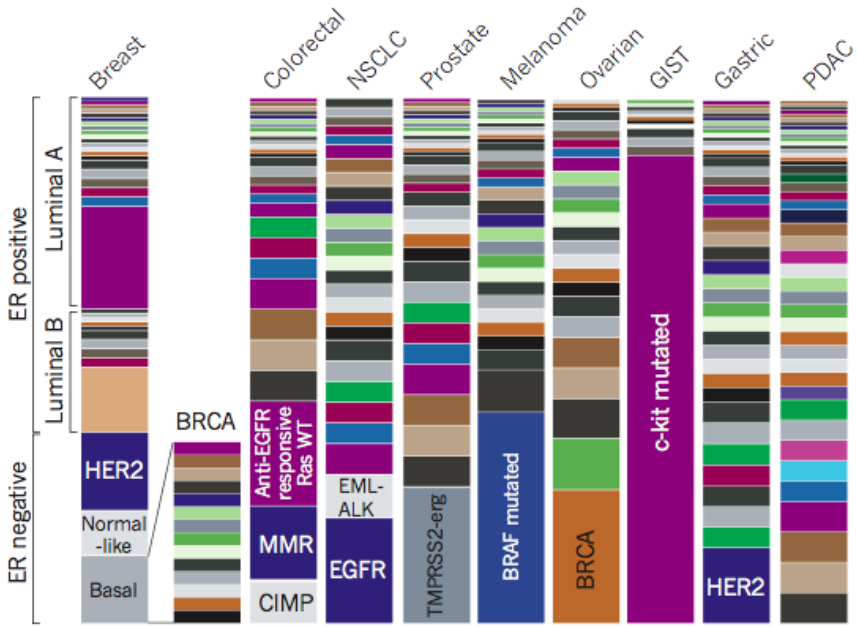
- **Rationale:**
  - Screening a large number of patients for multiple targets by a broad based platform reduces the screen failure rate
  - Provides a sufficient “hit rate” to engage patients and clinicians
  - Brings safe and effective drugs to patients faster

Requirements

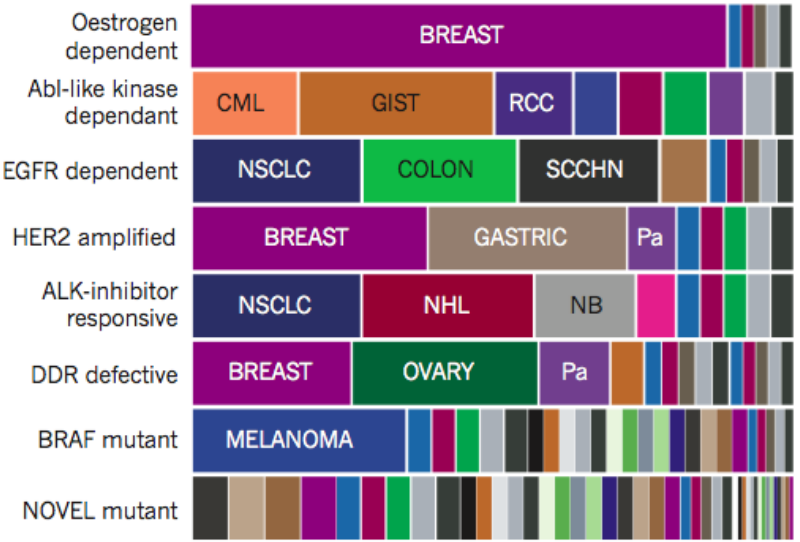
- Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection
- Develop a common protocol for the network that incorporates innovative statistical approaches to study design and data analysis
- Pharmaceutical industry partners
- Regulatory considerations

Address the expanding molecular taxonomy of cancers

Tumor of origin



Molecular characteristics



UMBRELLA PROTOCOLS

BASKET PROTOCOLS

Biankin et al. Nature 2015

Master Protocol: Umbrella vs. Basket Trial

Umbrella

Test impact of different drugs on different mutations in a single type of cancer

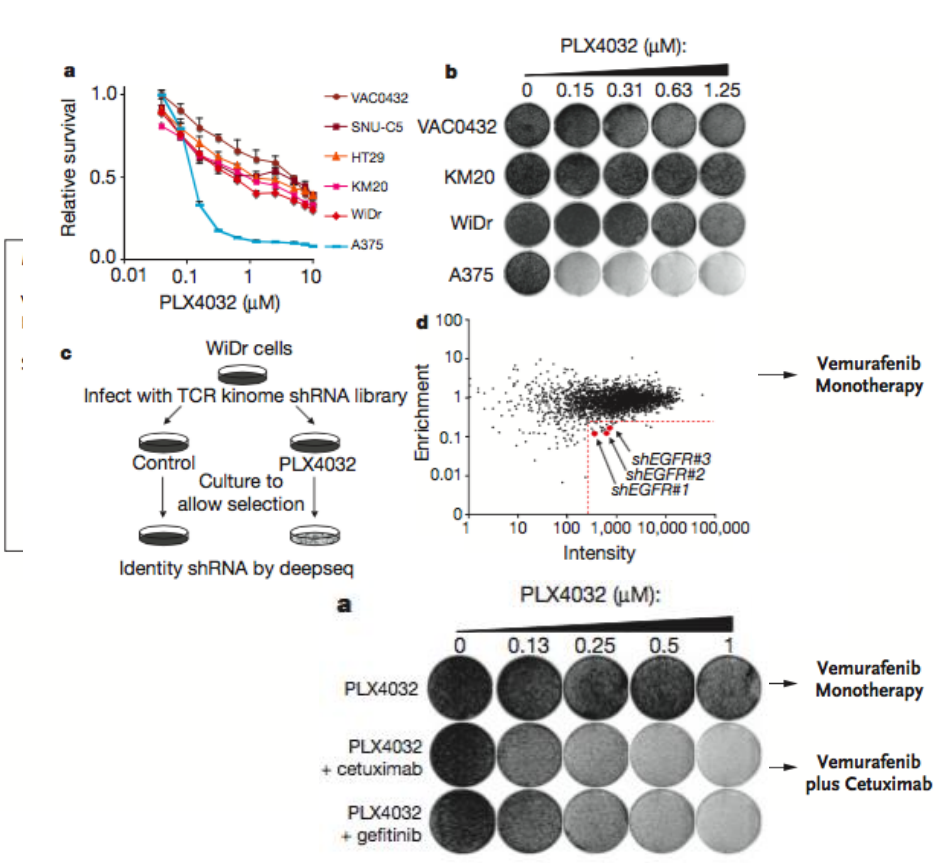
- BATTLE
- I-SPY2
- Lung-MAP Squamous Lung Master

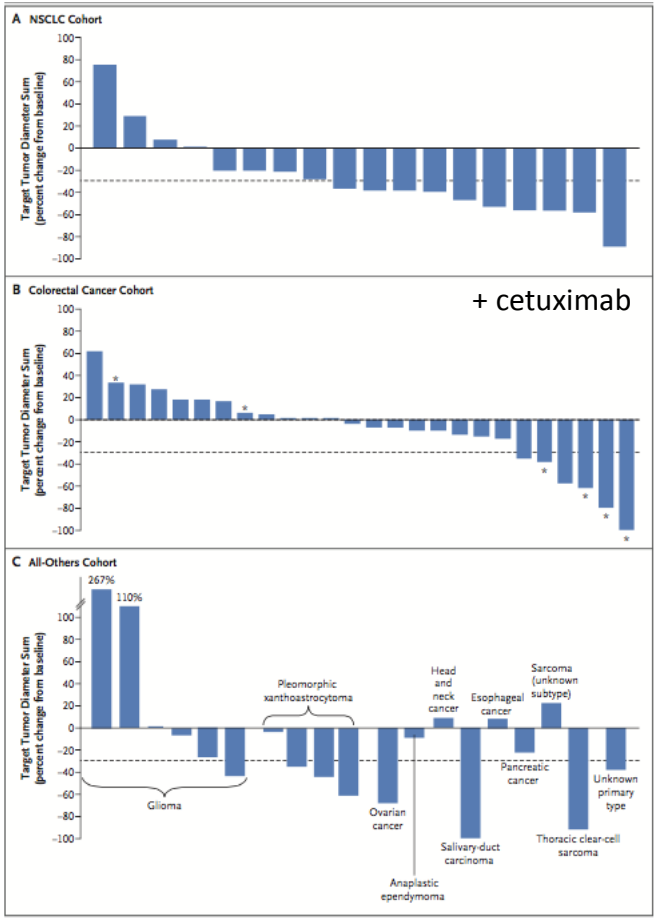
Basket

Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types

- BRAF V600X BASKET trial
- NCI MATCH

BASKET Trial: Vemurafenib in multiple non-melanoma cancers with BRAF V600 Mutations





Hyman et al, NEJM 2015; Prahallad et al. Nature 2012

Prospective Trial Design Considerations: Role of Biomarker

- **All-comers with biomarker stratification**:
  - Consider results combined and separately within biomarker-positive and -negative subgroups

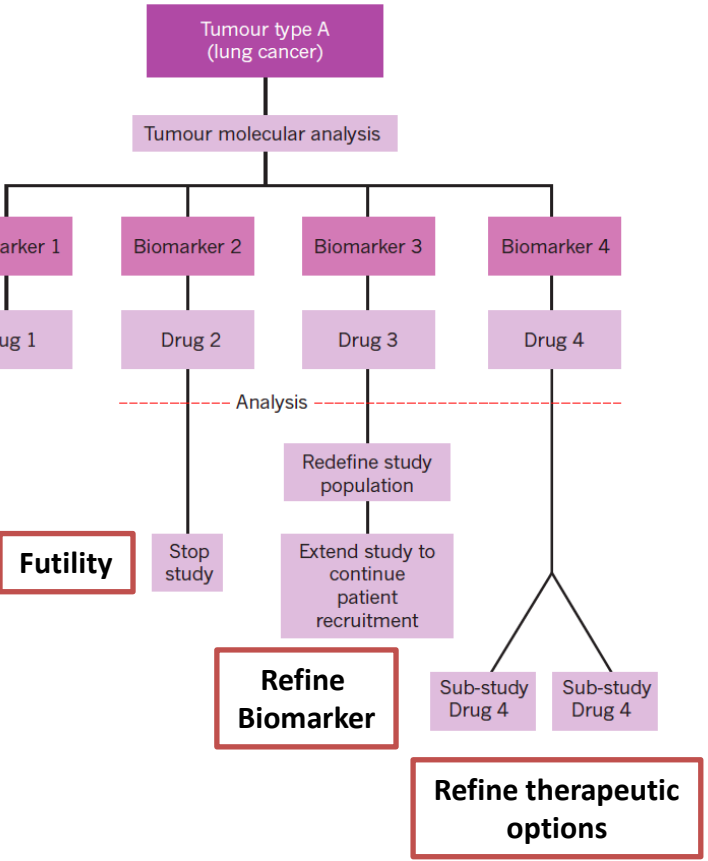
- **Biomarker enrichment**:
  - Biomarker positivity required for eligibility

- **Biomarker adaptive**:
  - Trial design features adapted during course of the trial depending on early results within biomarker-positive and negative subgroups

Umbrella adaptive designs

High precision biomarker →

Pharmacologic active Compound/ combination →



Biankin et al. Nature 2015

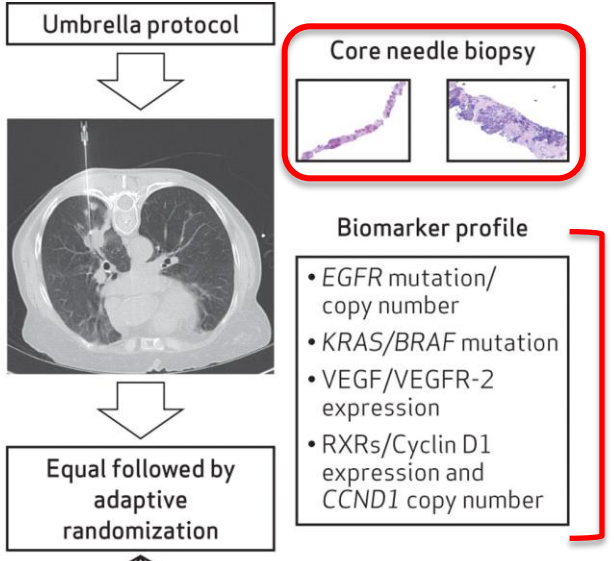
Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE)

Phase II "umbrella protocol" – patients with advanced NSCLC

Endpoint:

8 week disease control rate

DCR > 30%



Adaptive randomization

- More patients received more efficacious treatments

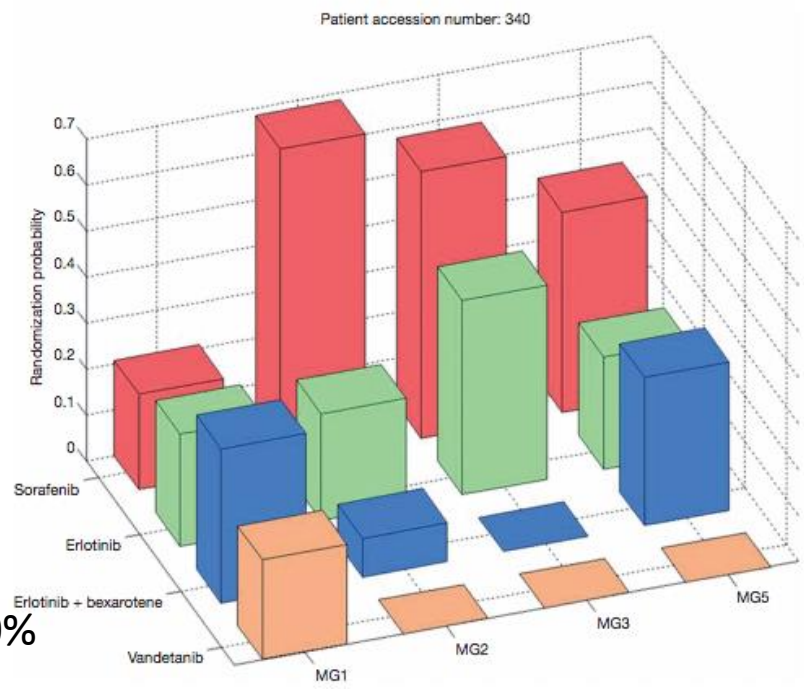
- **11 biomarkers**
- **2048 possible combinations!**

Bayesian adaptive design

- Early stopping rule for ineffective treatments

Kim et al. Cancer Discovery 2011

Randomization outcome of BATTLE-1



58%

34%

8 week DCR 50%

33%

Table 1 Marker group definitions in BATTLE-1

Marker group	Biomarkers			
	EGFR	*KRAS/BRAF*	*VEGF/ VEGFR*	*RXR*/cyclin D1
1	+	x	x	x
2	–	+	x	x
3	–	–	+	x
4	–	–	–	+
5	–	–	–	–

"+" is positive; "–" is negative; "x" is either positive, negative, or unknown; EGFR, epidermal growth factor receptor; BATTLE, Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination.

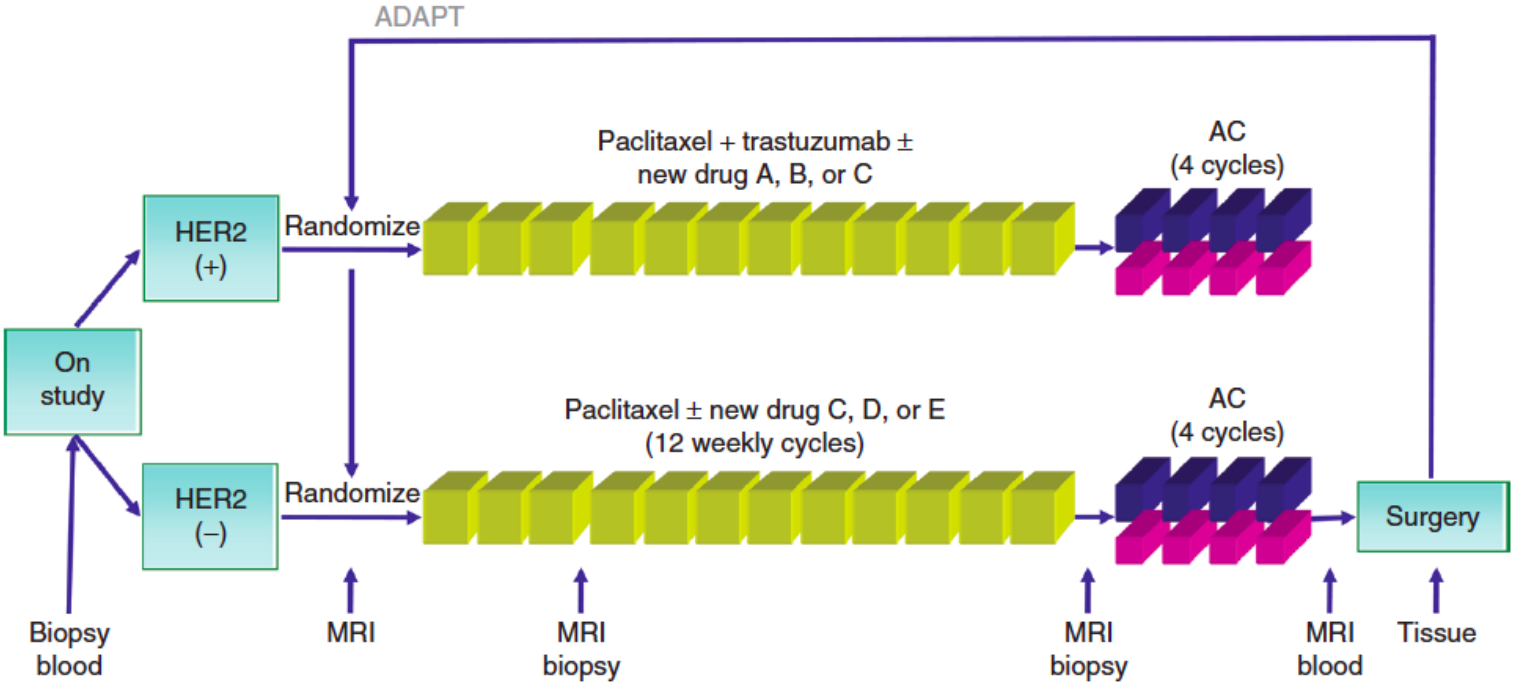
Liu and Lee CCO 2015

Precision-medicine clinical trials

Study	Tumour	Phase/design	Location	Arms	Patients†	Clinical trial ID	References
Bisgrove	All	Phase II, non-randomized	United States	N/A	84	NCT00530192	19
IMPACT	All	Phase I	United States	N/A	1,144	NCT00851032	20
MOSCATO 01	All	Phase I	France	N/A	420	NCT01566019	21
Lung-MAP	Squamous lung	Phase II/III, randomized	United States	5	10,000	NCT02154490	49
BATTLE	NSCLC	Umbrella, route to four phase II randomized	United States	4	300	NCT00409968 (umbrella) NCT00411671 NCT00411632 NCT00410059 NCT00410189	31, 66, 67
BATTLE-2	NSCLC	Phase II randomized	United States	4	450	NCT01248247	N/A
BATTLE-FL	NSCLC	Phase II randomized	United States	4	225	NCT01263782	N/A
I-SPY 2	Breast cancer	Phase II randomized	United States	8	800	NCT01042379	68, 69
NCI-MPACT	All	Phase II stratified, non-randomized	United States	6	700	NCT01827384	70
NCI-MATCH	Solid	Phase II stratified, non-randomized	United States	20	3,000	Umbrella, route to phase II‡	48
V-BASKET	All	Phase II stratified, non-randomized	Global	2	160	NCT01524978	71
CREATE	Selected	Phase II stratified, non-randomized	European Union	6	582	NCT01524926	N/A
WINTHER	All	Stratified, non-randomized	European Union	2	200	NCT01856296	72
SHIVA	All	Phase II stratified, controlled	France	10	1,000	NCT01771458	38
MOST	All	Phase II stratified, randomized	France	5	560	NCT02029001	N/A
SAFIR 02 Lung	NSCLC	Phase II stratified, randomized	France	8	650	NCT02117167	73
SAFIR 02 Breast	Breast cancer	Phase II stratified, randomized	France	18	460	NCT02299999	N/A
Lung MATRIX	NSCLC	Phase II stratified, non-randomized	United Kingdom	21§	2,000‖	EudraCT 2014-000814-73	65
FOCUS 4	Colorectal cancer	Phase II/III randomized	United Kingdom	4	643	EudraCT 2012-005111-12	74
IMPaCT	Pancreatic cancer	Phase II stratified, randomized	Australia	4	90	ACTRN 12612000777897	47

Biankin et al. Nature 2015

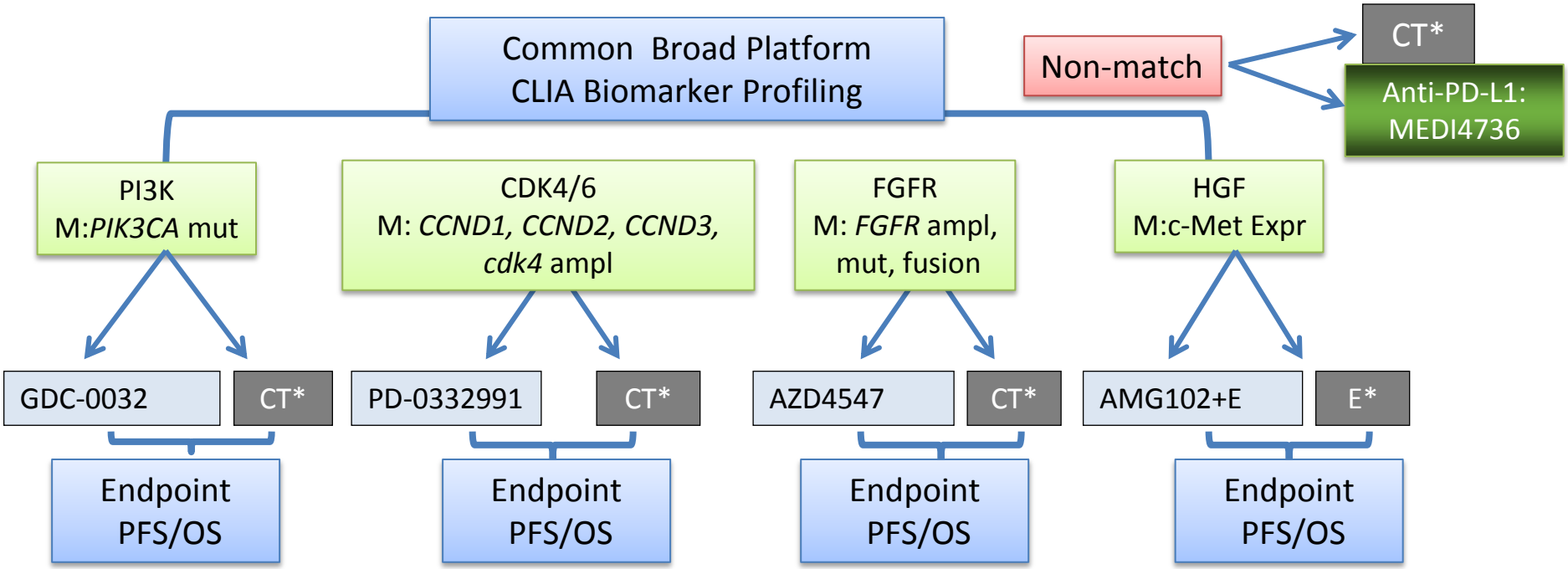
I-SPY 2 TRIAL



Barker et al. Clin Pharm Therapeutics 2009

S1400

LUNG-MAP



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

Archival FFPE tumor, fresh CNB if needed

Conclusions

- **Innovative trial designs, e.g., umbrella or basket protocols, will be increasingly common in the future**

- **Biomarkers must be critically evaluated**
  - Performance and precision

- **Trial networks with established infrastructure and use of a common protocol can address many of the challenges**
  - Optimize trial design and conduct to realize efficiencies
  - Improve data quality through centralization of processes, systems, and training