GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

ESMO 2014

Overview of trials testing tumour molecular profiling:

lung cancer as a model

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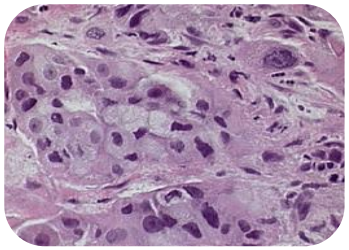
Inserm
Institut national
de la santé et de la recherche médicale

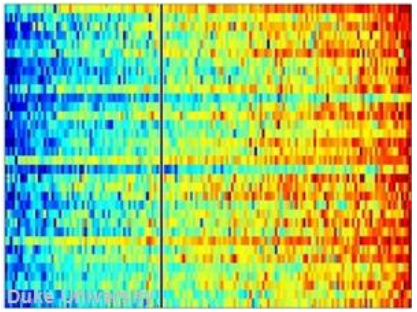
The aim of molecular profiling trials

Patients with lethal NSCLC

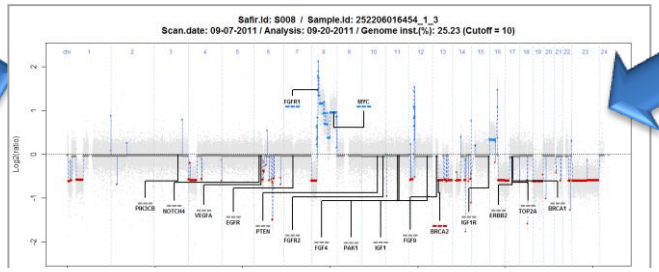


Tumor Specimen

Molecular profiling



Intelling reports



Targeted therapy according to the molecular profile

How can molecular profiling help the oncologist understand the biology in each patient in order to better treat him ?

General goals of tumour molecular profiling

- Tumour molecular profiling can help decipher cancer biology at the individual level and identify:

  → **Oncogenic drivers and predictors of efficacy**

  → Lethal subclones & intratumor heterogeneity

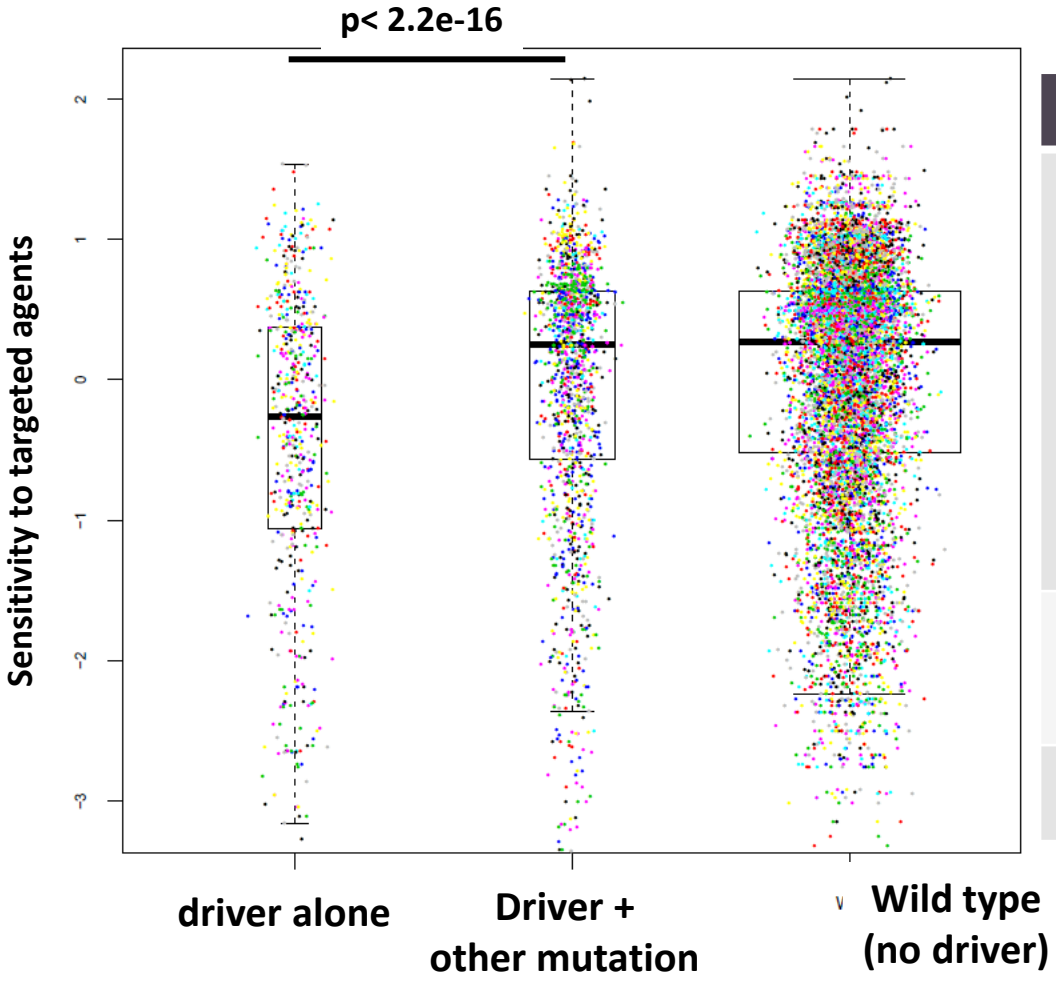
  → Mutagenesis processes & DNA repair defects

  → Dialogue between cancer cells and immune system

Challenges of tumour molecular profiling

- Various models of implementation in the clinical setting
- The optimal technology is yet to be universally adopted
- The optimal setting for analysis (metastatic vs locoregional vs resected) is still debated
- Best patient population to enroll (refractory, sensitive…) TBD
- Access to therapies (and notably combinations) is a problem

Co-existing mutations: a major challenge?



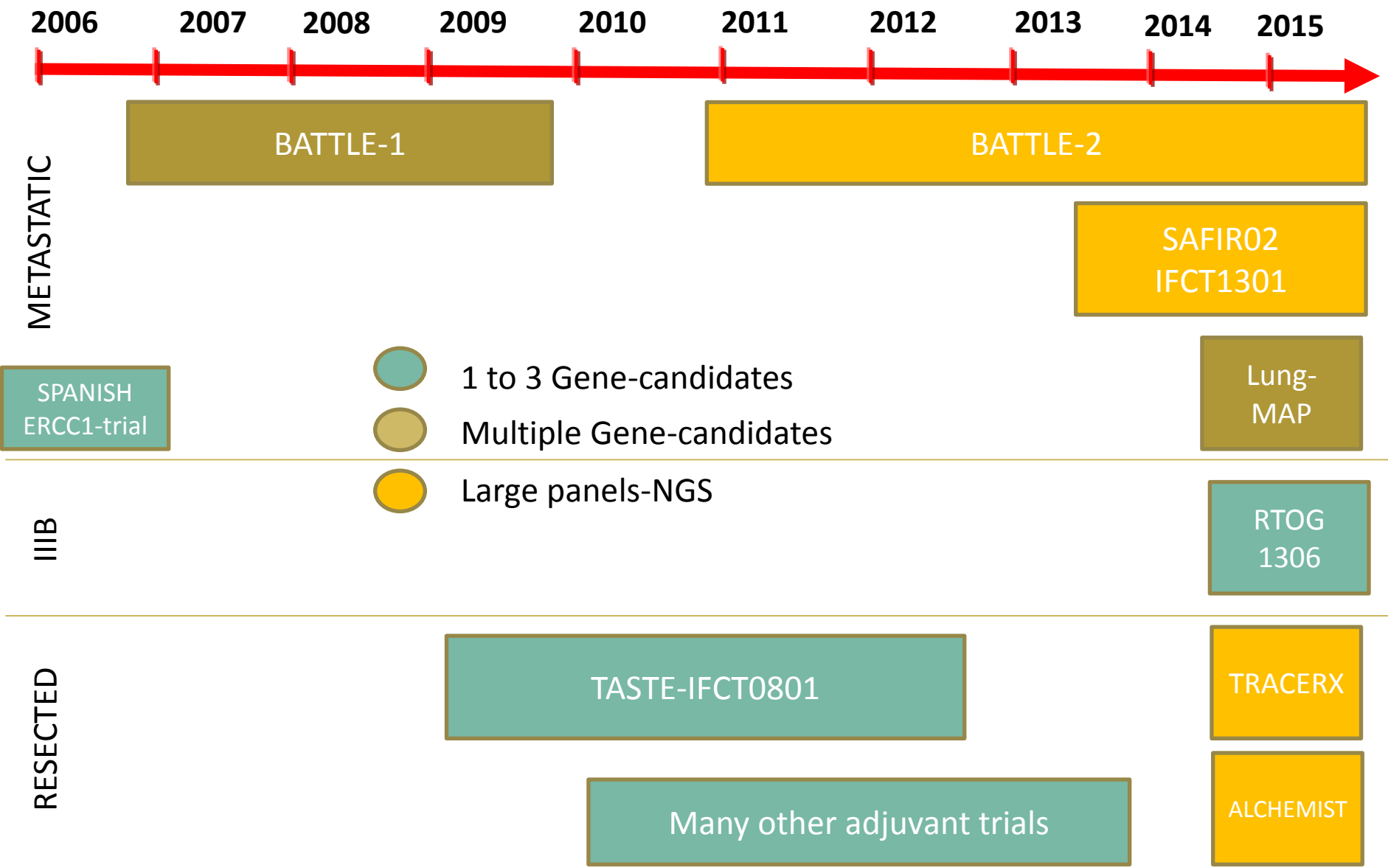
	In Cell lines
Source	• **GDSC (**Genomics of Drug Sensitivity in Cancer) 80 drug-gene-alteration pairs for 20 drugs and 19 targetable genes • **CCLE** (Cancer Cell Line Encyclopedia) 16 drug-gene-alteration pairs for 4 drugs and 5 targetable genes
Gene alteration	• **Mutation** • **Amplification (CNV > 4)** • **Loss (CNV < 2)**
Drug response	**nAUC** (Scaled AUC)

Each color represent one drug/target couple

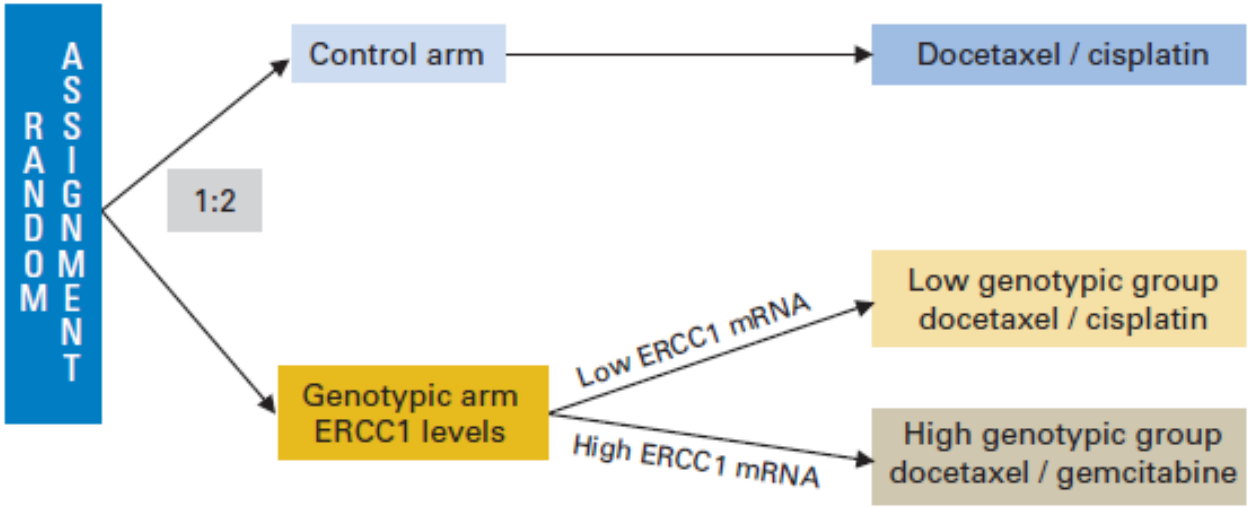
Co-existing mutations are associated with resistance

Lefebvre & Yu Cancer Pharmacogenomics and Targeted Therapies 2014

Partial perspective of molecular profiling trials in lung cancer



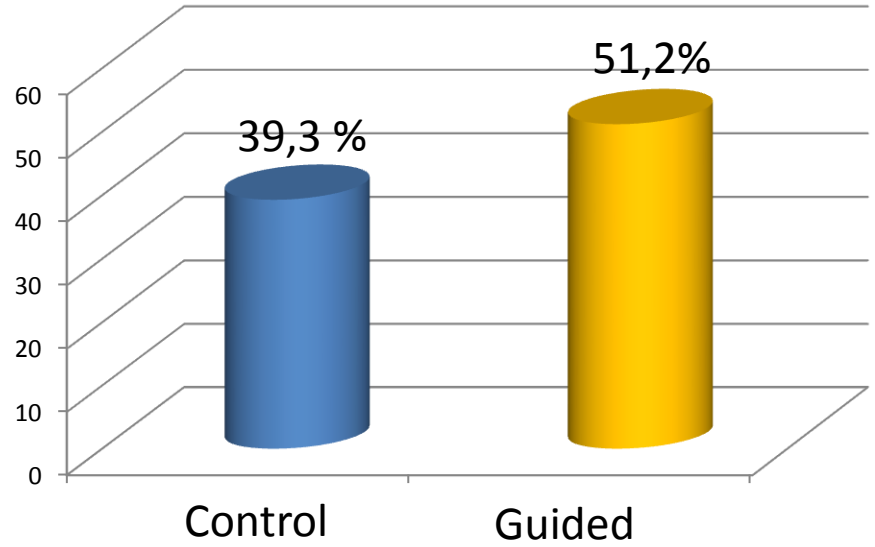
GILT: the 1st prospective customized trial



August 2001
October 2005
N = 444 patients
24 sites (Spain)

PI: R Rosell

ORR



But

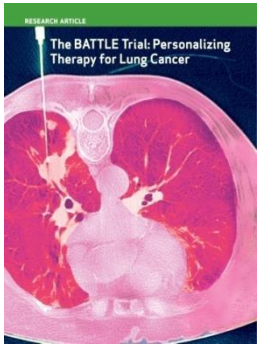
- ❖ No PFS or OS difference…
- ❖ 17% rate of screen-failures

- ❖ Prospective FFPE analysis with microdissection and RT-PCR…

BATTLE1

Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination

- Platform for integrated translational research
  - → Clinical trial program
  - → Novel trial design
  - → Biomarker discovery

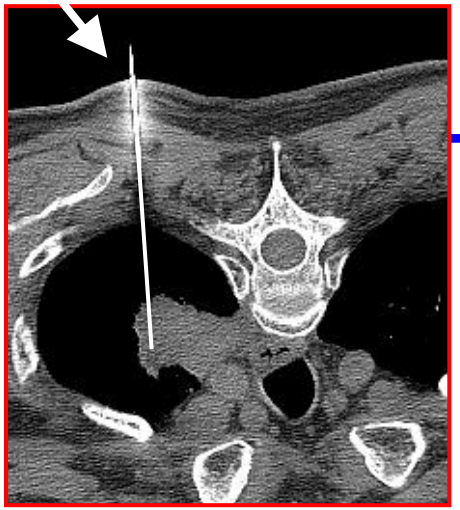


- Scientific Hypotheses
  - → Real time biopsies are possible to more accurately reflect aberrant signaling pathways of lung cancer
  - → Matching targeted agents with abnormal pathways will improve disease control in lung cancer patients
  - → 8-week disease control is an acceptable surrogate for efficacy (OS) in patients with pretreated lung cancer

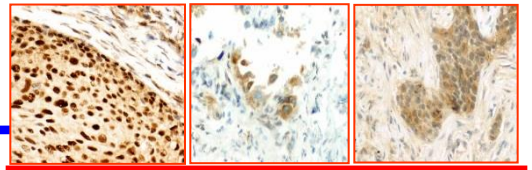
E. Kim et. al, Cancer Discovery 2011

BATTLE 1 Schema

Umbrella Protocol

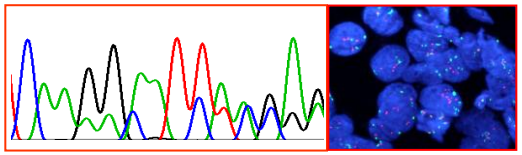


Core Biopsy



Biomarker Profile

EGFR KRAS/BRAF
VEGF RXR/CyclinD1



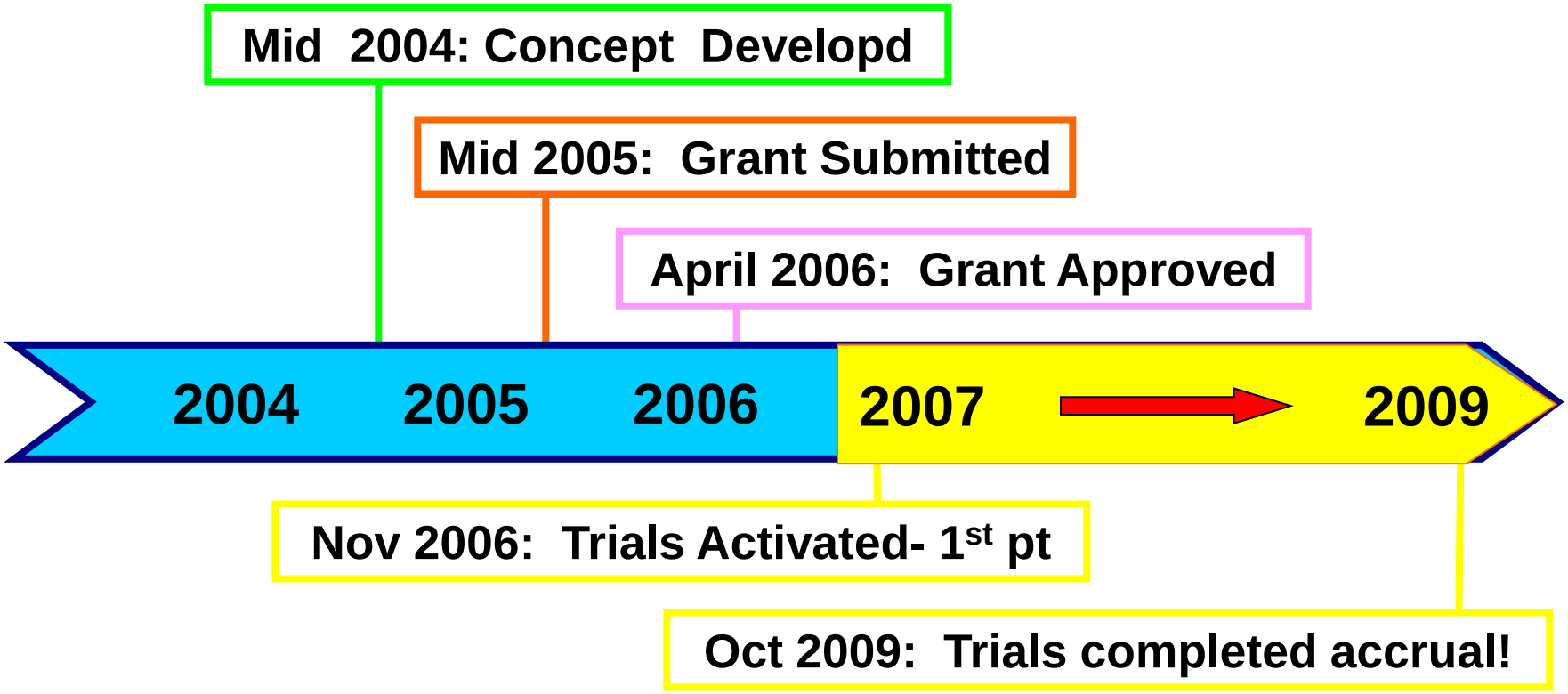
Randomization:
Equal → *Adaptive*

Erlotinib | Vandetanib | Erlotinib + Bexarotene | Sorafenib

Primary end point: 8 week Disease Control (DC)

Kim E et al AACR 2010

BATTLE-1 Timelines



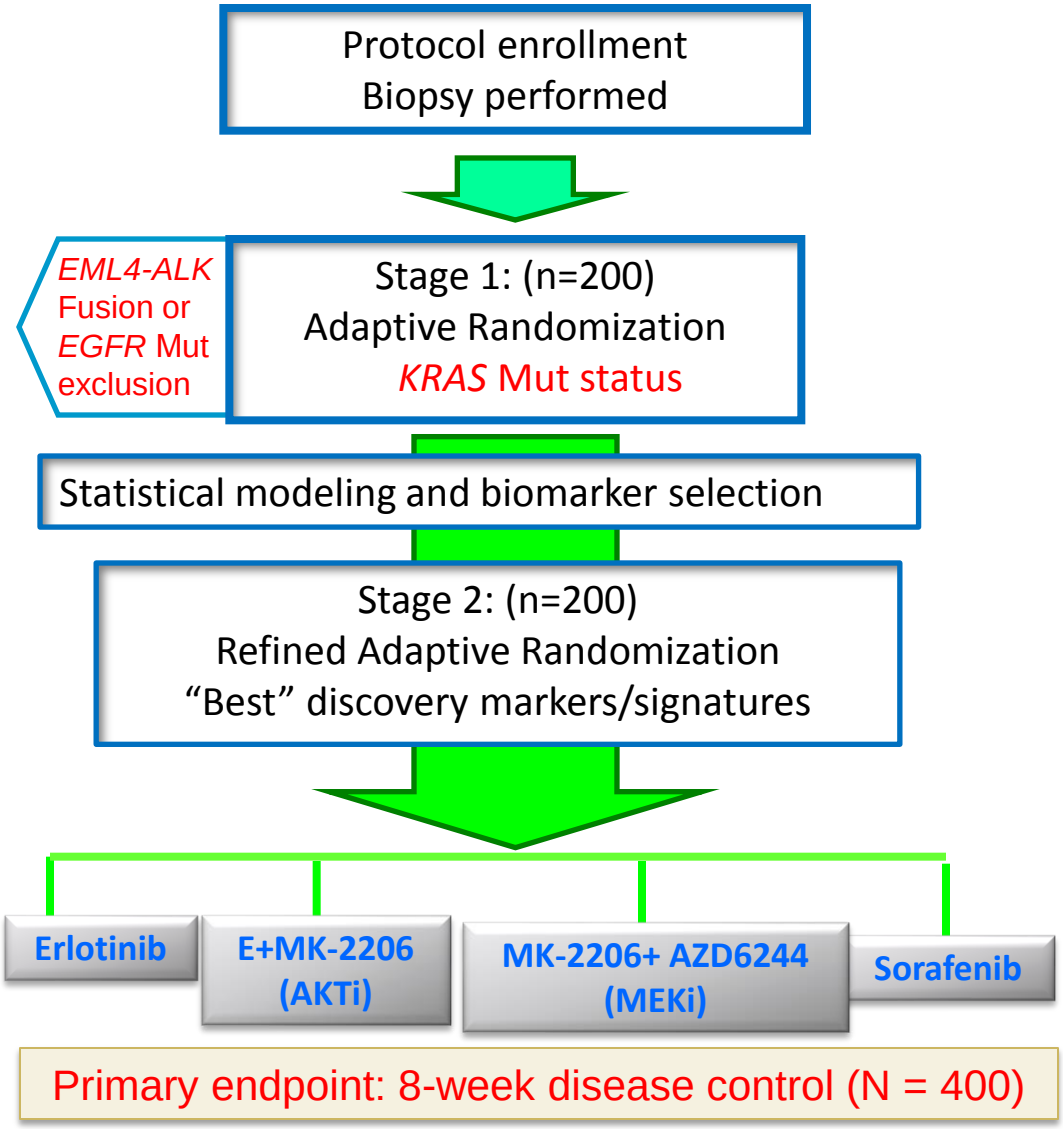
Courtesy WK Hong

Assessment of BATTLE-1 Trial

- Successful completion of a *prospective*, biopsy-driven, study in lung cancer
  - → This is now an acceptable approach!
- Patients are guided toward more effective personalized treatments (Adaptive design)
- Traditional way to identify biomarkers
  - → *Retrospective* analysis of patient archives sample
- The *new* way
  - → *Prospective* biomarkers evaluation
  - → Unprecedented biospecimen resources for discovery

Courtesy WK Hong

BATTLE-2 Trial



Biomarkers:

- Protein expression (IHC): 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®
- Protein profiling – RPPA (n=174)
- NGS-Foundation Medicine
- RNA sequencing

Courtesy V Papadimitrakopoulou

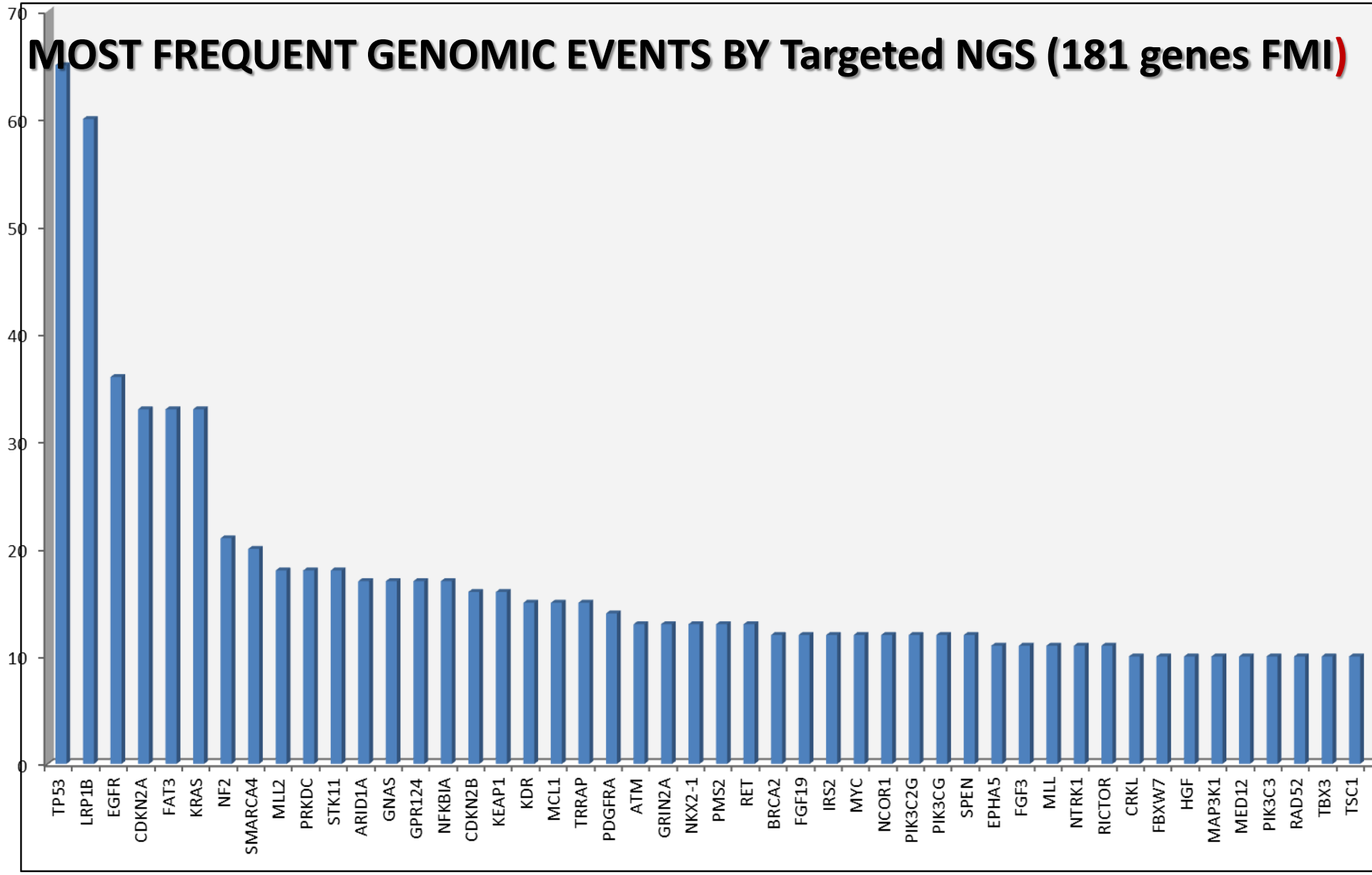
Updated Accrual 05/30/2014

Trial activation **MDACC: June 2011** **Yale: August 2012**

	Total by Site		Total
	MDACC	Yale	
Patients screened	604	70	674
Patients consented &registered	276	56	332
Biopsies performed	234	41	275
Screen Failures	105	27	132
Patients Randomized	176	32	208
Patients Treated	171	29	200
Tx Erlotinib (Arm 1)	17	5	22
Tx Erlotinib/MK-2206 (Arm2)	36	6	42
Tx MK-2206/AZD6244 (Arm 3)	64	11	75
Tx Sorafenib (Arm 4)	54	7	61
Primary endpoint reached	161	26	187

Courtesy V Papadimitrakopoulou

MOST FREQUENT GENOMIC EVENTS BY Targeted NGS (181 genes FMI)



Courtesy WK Hong and V Papadimitrakopoulou

Primary endpoint BATTLE-2

Response

By arms

8 week response	Arm1	Arm2	Arm3	Arm4	Total
PR	1(5.0%)		3(4.3%)	3(4.9%)	7(3.7%)
SD	6(30.0%)	18(50.0%)	34(48.6%)	25(41.0%)	83(44.4%)
PD	13(65.0%)	18(50.0%)	33(47.1%)	33(54.1%)	97(51.9%)
Non Evaluable	2	6	5	0	13

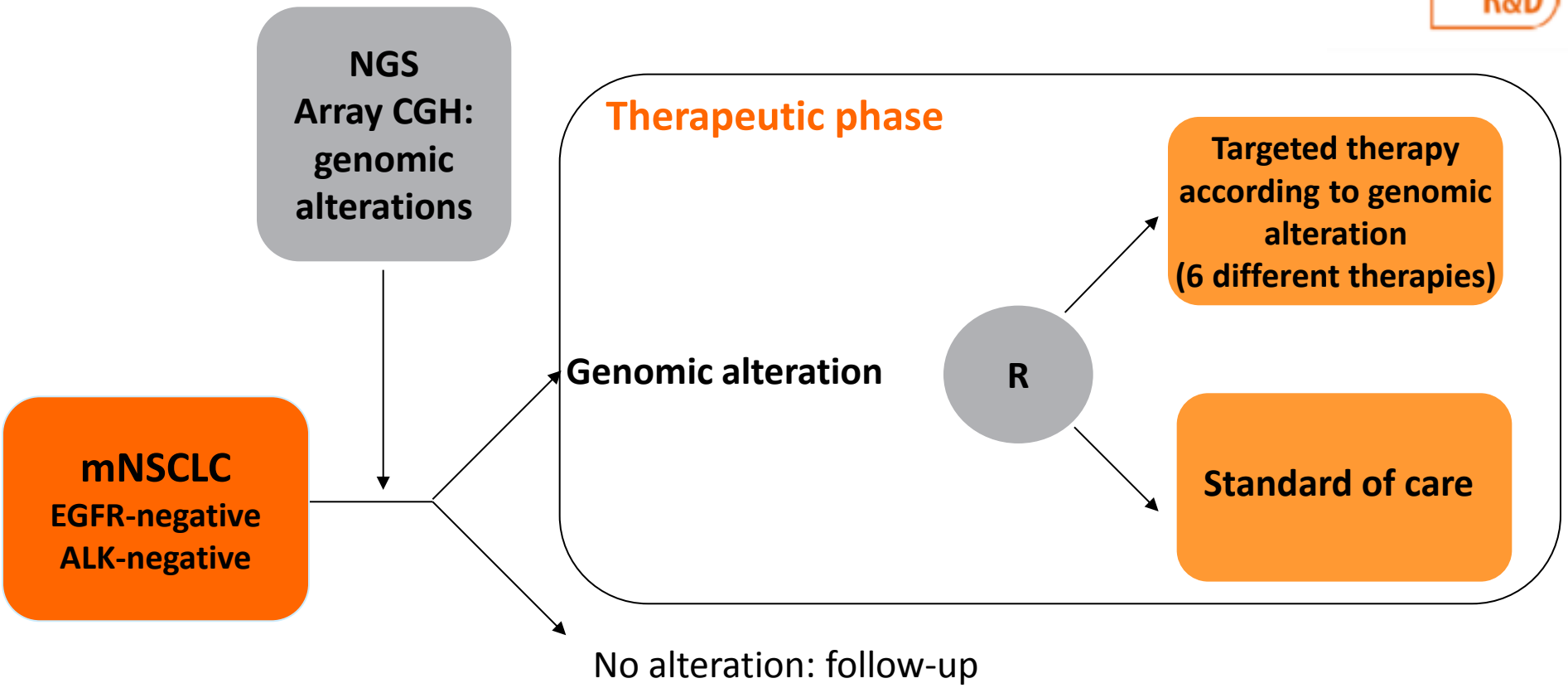
8-wk DC

8 week disease control	E(1)	E+M (2)	M+A (3)	S	Total
8wk DC	7(35.0%)	18(50.0%)	37(52.9%)	28(45.9%)	90(48.1%)
No 8wk DC	13(65.0%)	18(50.0%)	33(47.1%)	33(54.1%)	97(51.9%)
P (Fisher's exact test)		.40	.20	.44	

Courtesy V Papadimitrakopoulou

Design of the SAFIR02 lung-IFCT1301 trial

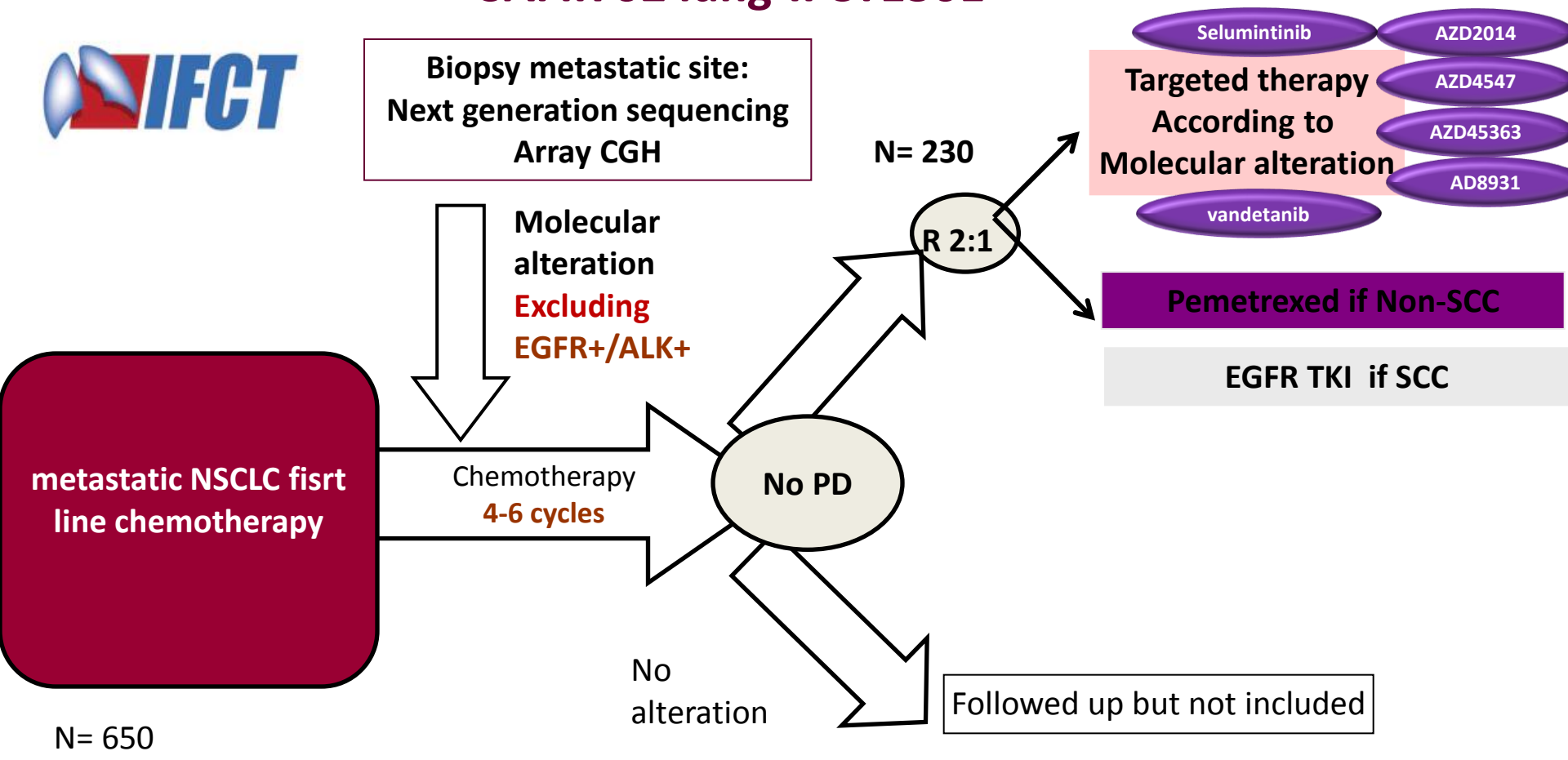
IFCT 13-01



Sponsor: UNICANCER-IFCT
Partnership: AstraZeneca & French Charity Foundation ARC

PI: JC Soria
Co-PI: F Barlesi

SAFIR 02 lung-IFCT1301

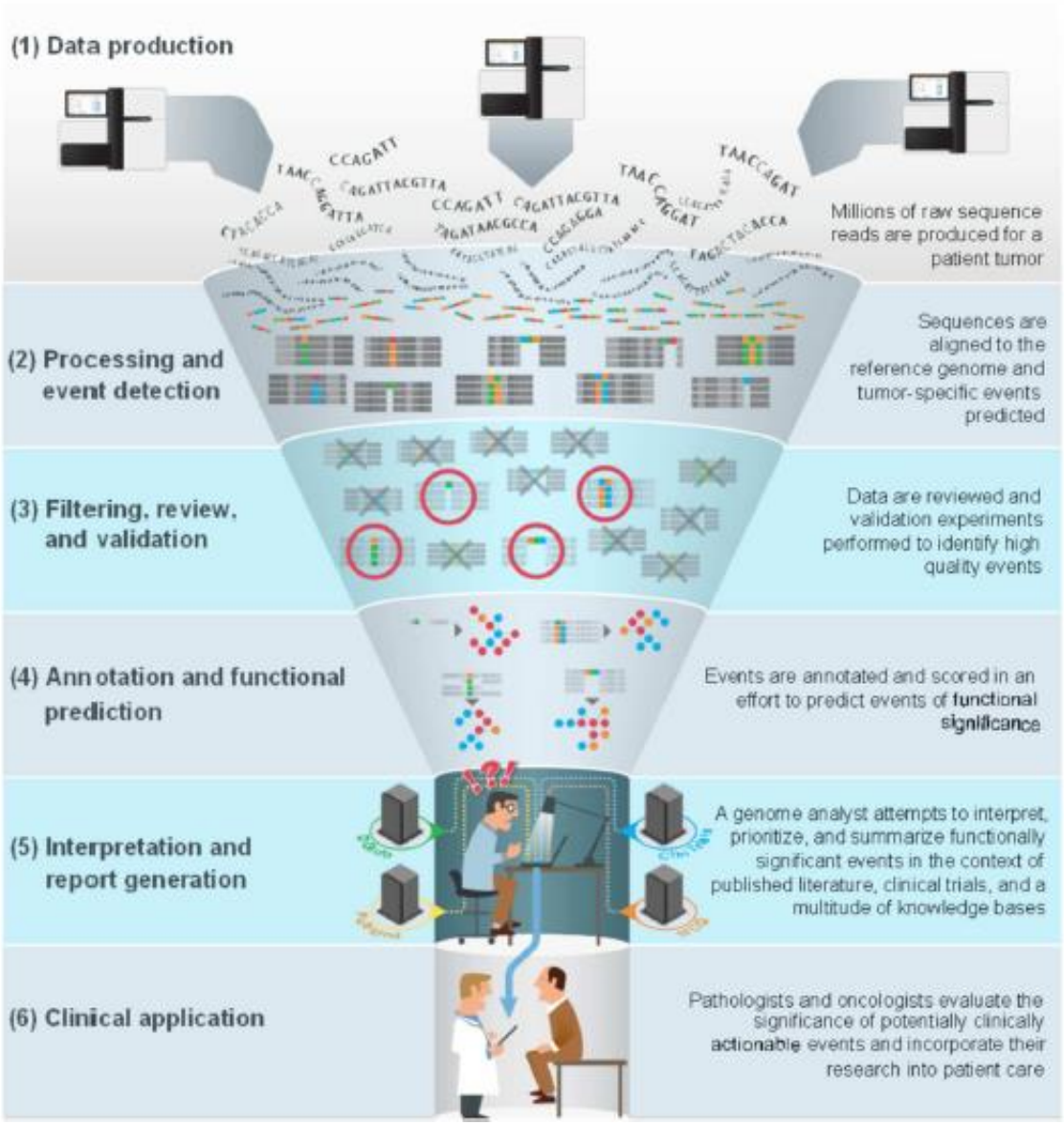


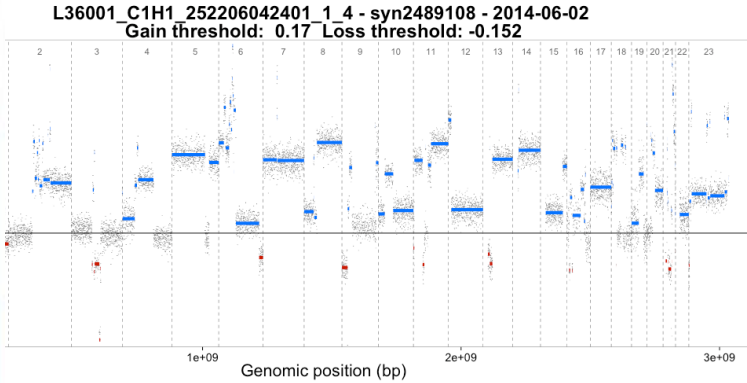
All histologies

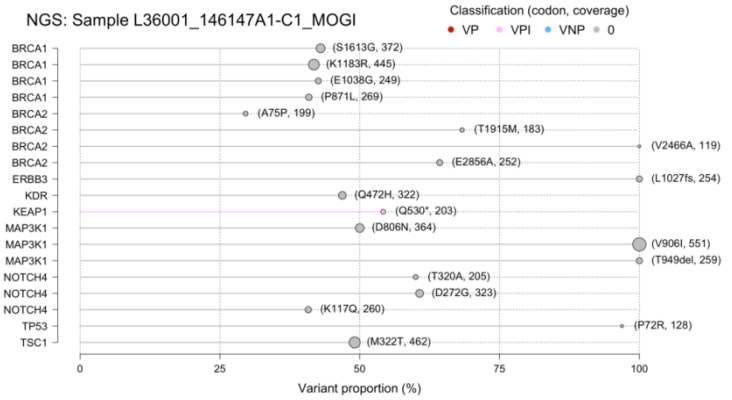
Ethics approval sept 2013; ANSM approval oct 2013

SAFIR 02 lung-IFCT1301 sites

SAFIR 02 lung-IFCT1301 data interpretation challenge

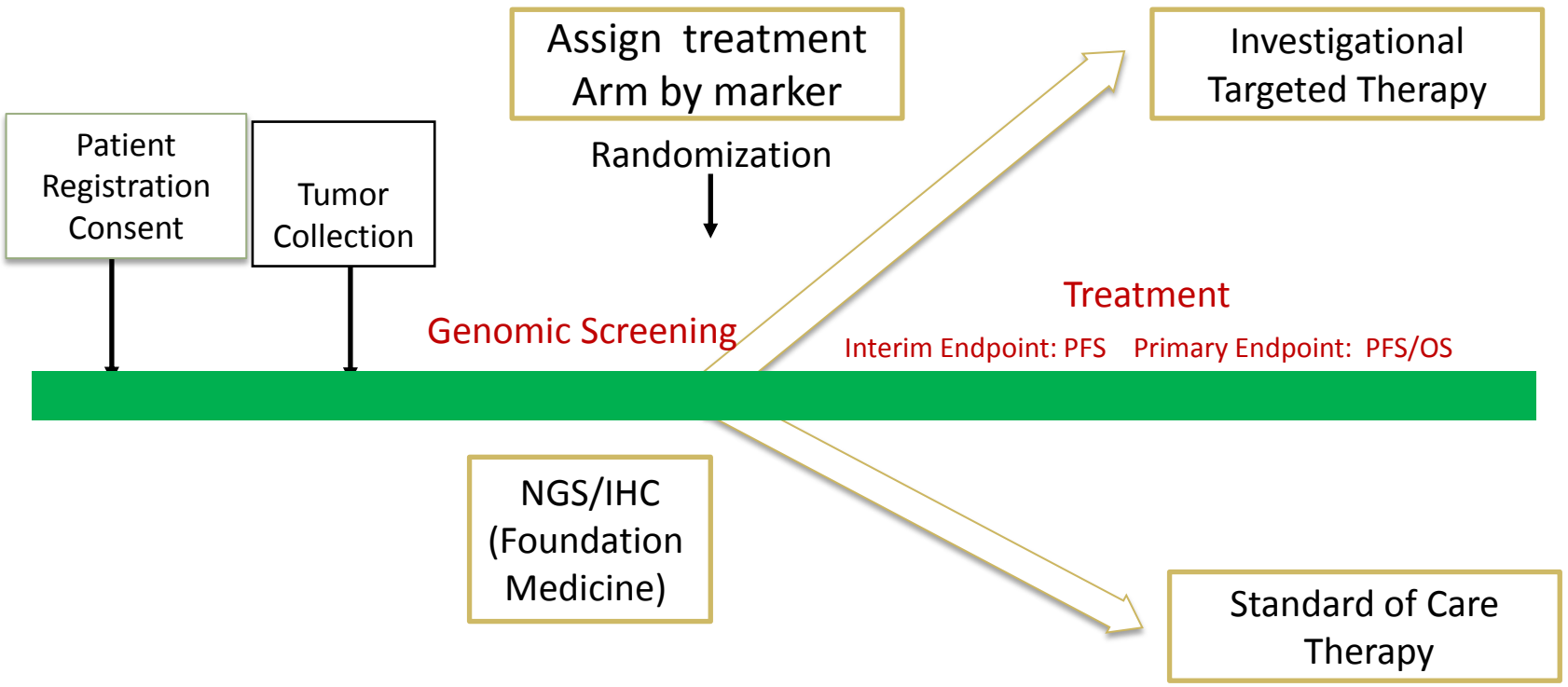




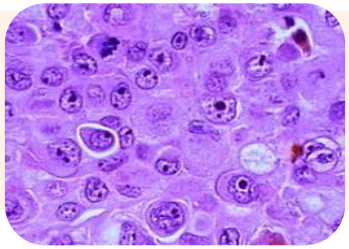


Good et al. Genome Biology 2014, 15:438

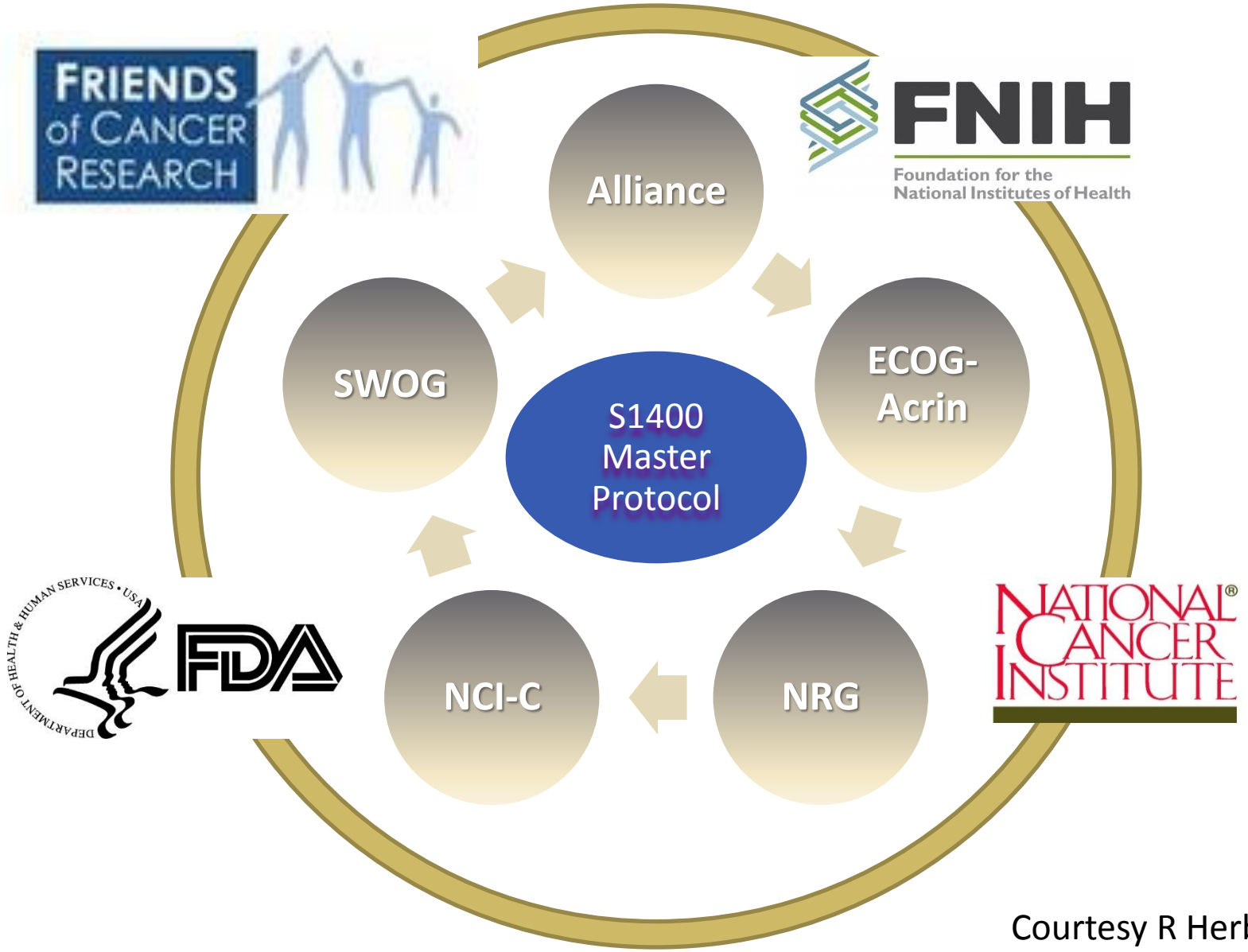
LUNG-MAP



Squamous cell carcinoma 30%



Lung-MAP partners



Courtesy R Herbst

Lung MAP Will be Run Throughout the US- 500+ sites

Courtesy R Herbst

Molecular read-out

Foundation Medicine NGS test platform (CLIA/CAP)

Classification rules

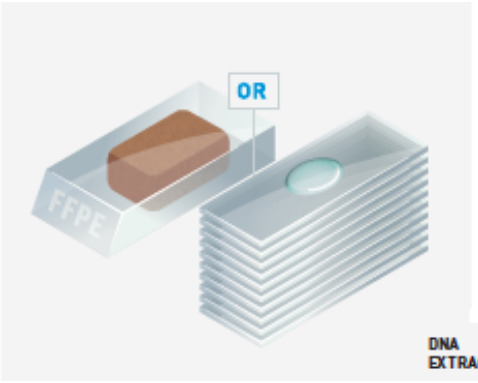
1) DNA extraction

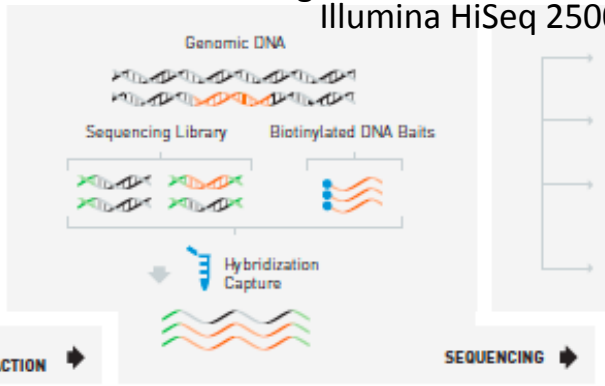
2) Library construction: selected cancer genes

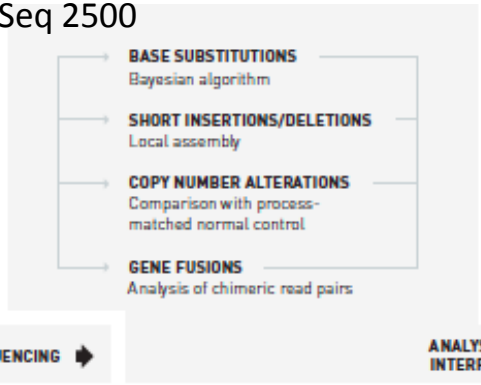
Illumina HiSeq 2500

3) Analysis pipeline

4) Master protocol CTA







- Based on FM T5 NGS platform
- Implemented as “mask” of T5 content and classification rules on called alterations
- Rules determine biomarker positive/negative status

Non-NGS biomarkers:

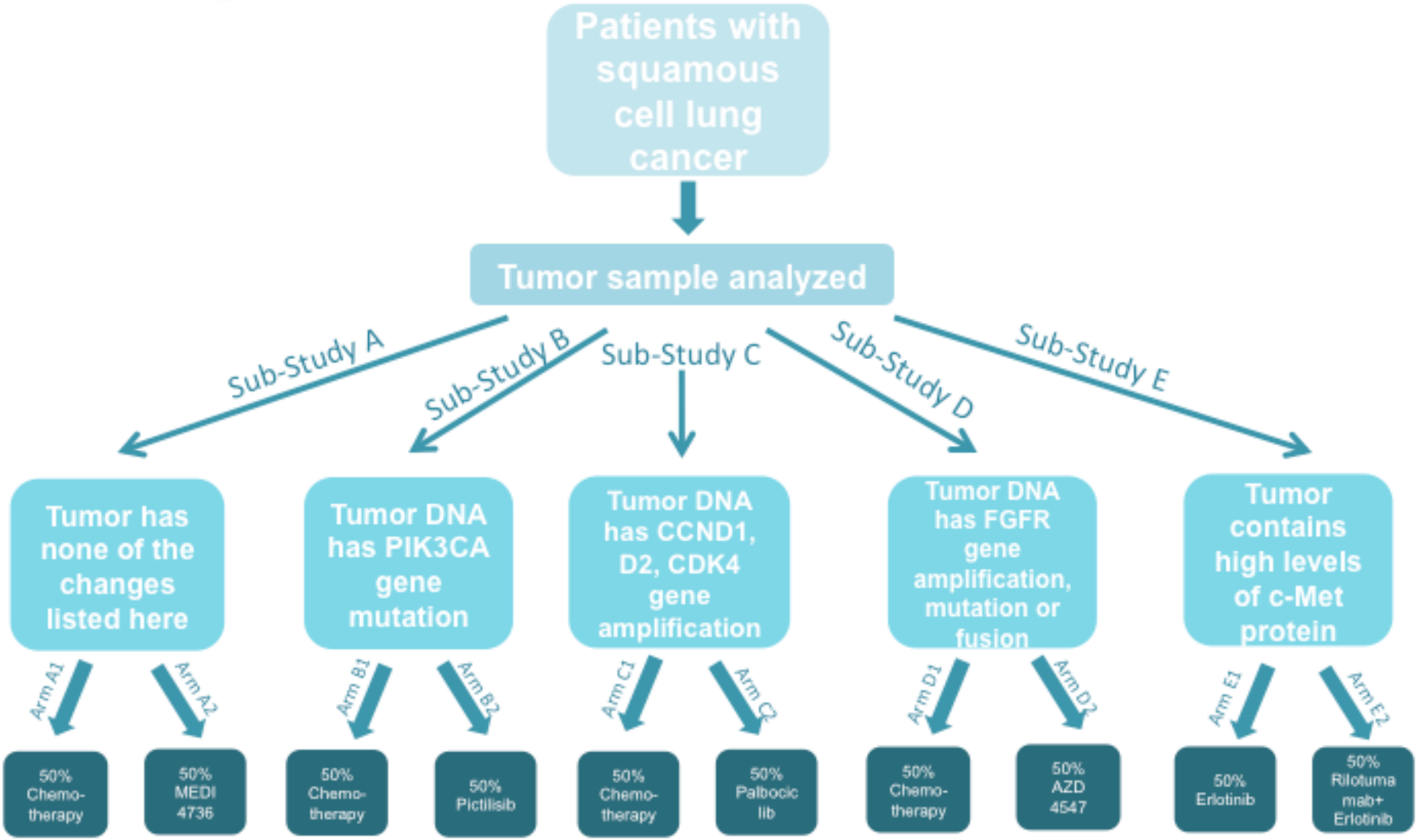
Supplementary assays	Non-match arm
MET IHC (+)	All assays (-)
MET pathway inhibitor	Anti-PD-L1 Ab

Classification rules (preliminary)

PIK3CA mutation	CCND1 amplification or CDKN2A/B deletion, and RB1 wild-type	FGFR1/2/3/4 amplification, mutation or fusion
PI3K inhibitor	CDK4/6 inhibitor	FGFR inhibitor

Courtesy R Herbst

Lung-MAP Sub-Studies for Treatment



Individualized Combined Modality Therapy for Stage III NSCLC RTOG 1306/Alliance 31101

Stratification

Mutation Type	**Weight Loss** (in prior 6 mos.)
1. EGFR	1. ≤ 5%
2. ALK	2. > 5%

EGFR TK Mutation Cohort

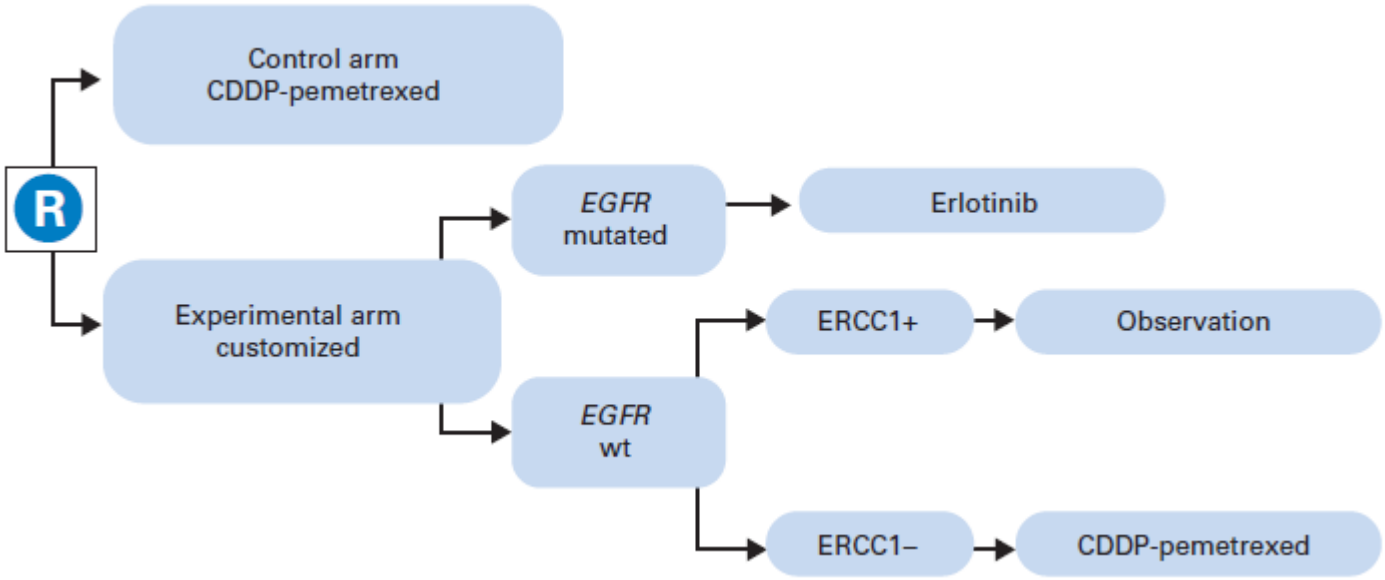
Arm 1: Erlotinib, 150 mg/day for 12 weeks → Concurrent chemotherapy and radiation, 64 Gy

Arm 2: Concurrent Chemotherapy and radiation, 64 Gy

Courtes y E Vokes

TASTE-IFCT0801: design

- TAilored post-Surgical Therapy in Early stage NSCLC
  - is a prospective, randomized, and customized trial
  - incorporating ERCC1 IHC status and EGFR mutational status

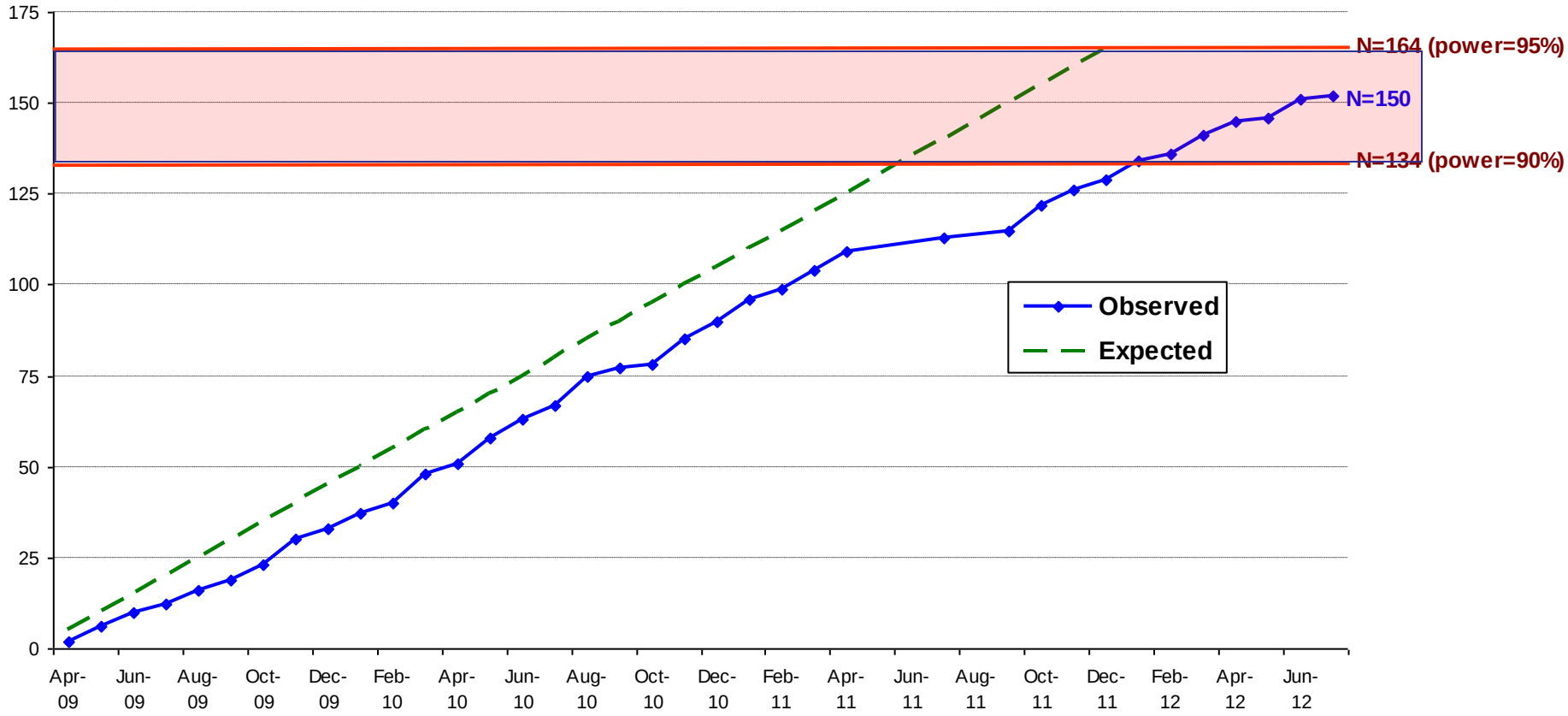


Stage II and IIIA (non-N2) NSCLC patients with non-SCC histology were allowed

This french national-wide initiative (IFCT) recruited 150 pts in 3 years

Wislez et al JCO 2014

TASTE-IFCT0801 recruitment



150 pts were randomized between May 2009 and July 2012 across 29 centers

TASTE-IFCT0801: Conclusions

- This adjuvant trial met its primary end point
  - for its phase II component
  - demonstrating the feasibility of a national biology-driven trial in the adjuvant setting.

- Safety data demonstrated an excellent tolerability profile for cisplatin-pemetrexed (as compared to cisplatin-navelbine).

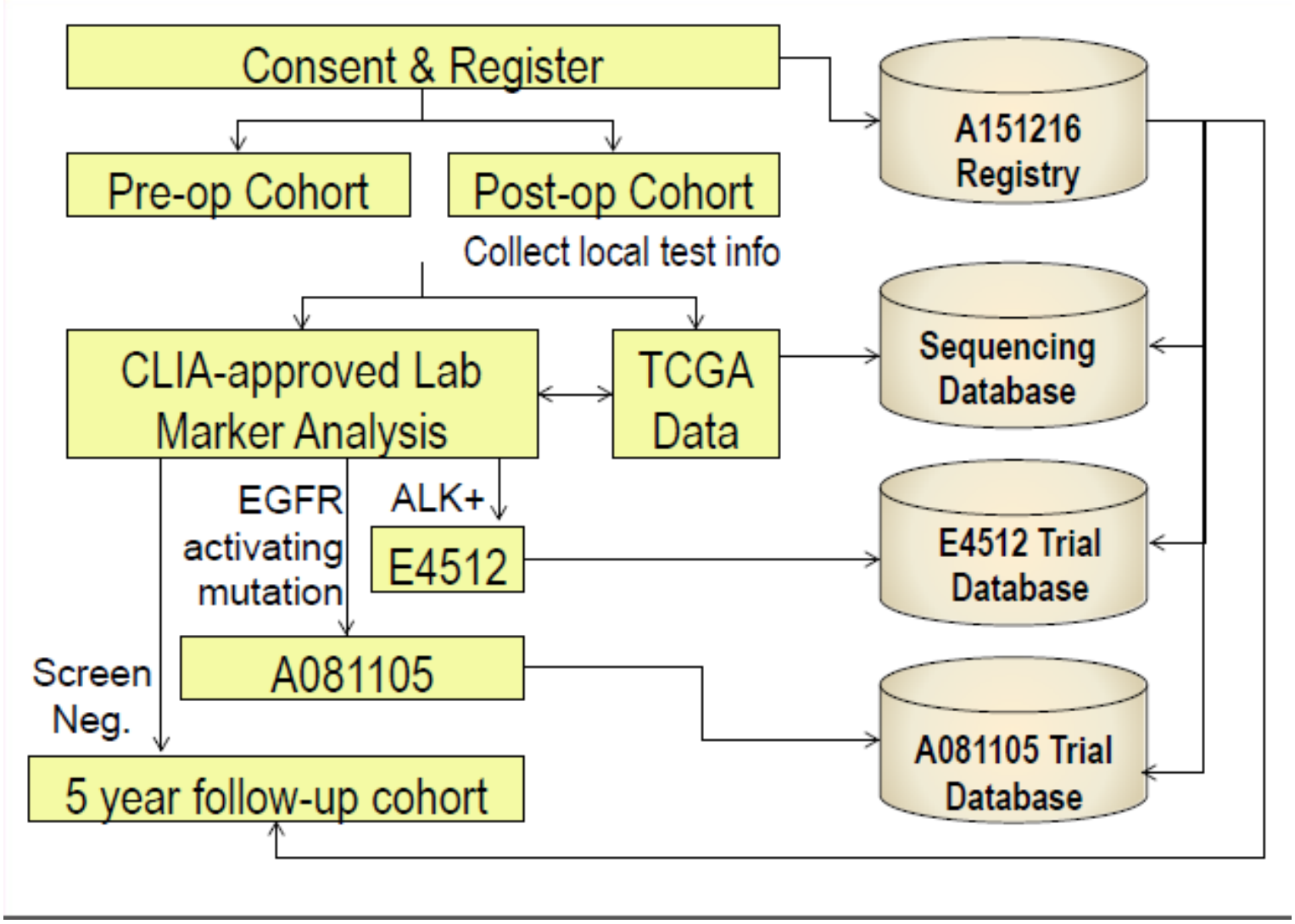
- The phase III component was canceled due to the unexpected unreliability of the ERCC1 IHC read-out.

- **ERCC1 IHC read-outs need to be refined before a prospective phase III trial is launched.**

ALChEMIST Adjuvant Lung Cancer Enrichment Marker Identification Sequencing Trial

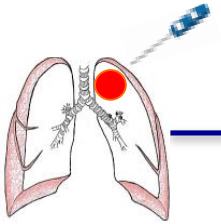
	ALCHEMIST SCREEN Component A151216	ALK+ E4512	EGFR-mutant A081105
Target	Registry	ALK+	EGFRmut
Prevalence	All comers	~5%	~10%
n	6000-8000	336	410
Primary Endpt	--	DFS-OS	OS
Power	--	80%	85%
One-sided α	--	0.025	0.05
HR	--	0.67	0.67
Adjunct	Extended sequencing for additional targets (TCGA) ; correlation with local testing	Peripheral screening for ALK; RTPCR to identify fusion partners	Targeted sequence and kinome analysis; PRO and QOL

ALChEMIST data flow

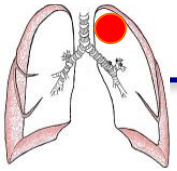


TRACERx Tracking Lung Cancer Evolution through Therapy/Rx

Clinical

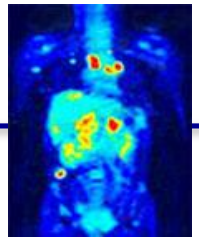


Biopsy (diagnosis)



Surgery

Adjuvant chemotherapy



Biopsy (progression)

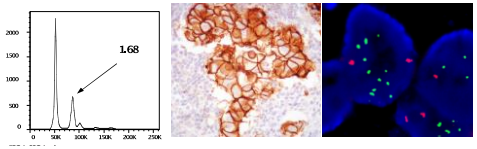
Clonal Dominance Clinical Studies

Functional imaging

UCL-AD — 48 gene panel

Molecular Pathology

Analyses of multiple regions of the tumour to assess genomic instability



- FACS – DNA ploidy analysis
- IHC – Tumour grade/nuclear pleomorphism
- FISH – chromosomal instability

Next generation sequencing

From multi region primary and metastatic samples:

- Whole exome & whole genome 'skim' sequencing
- Somatic point mutations, indels, structural changes
- Construct phylogenetic tree of the tumour sectors
- Compare ITH/genomic stability indices to drug resistance and outcome

Technology Development

Plasma samples for ctDNA → Track Cancer Evolution

Integration of clinical and genomic data

UCL-AD 35 Gene NGS Screen*

UCL Advanced Diagnostics

FFPE Tissue Block

Tissue curls sectioned (under clinical conditions) x4 10um curls in total.

DNA (x2 10µm section)

RNA (x2 10µm section)

Samples extracted, prepped and sequenced for mutations (DNA) and Translocations/CNV/Amp (RNA) on Ion Torrent.

EGFR, KRAS, BRAF, ALK, HER2, MET, IDH1, IDH2, PTCH1, ROS-1, KIT, NRAS, PIK3CA, PTEN, TP53, TMPRSS-ERG, H-RAS, MEK1, AKT1, PDGFRA, FGFR1, FGFR2, FGFR3, FGFR4, SMO, HER2, PIK3R1, DDR2, MYC, RB1, CTNNB1, ABL1, MPL1, RET1

Integrated Cancer Panel Report

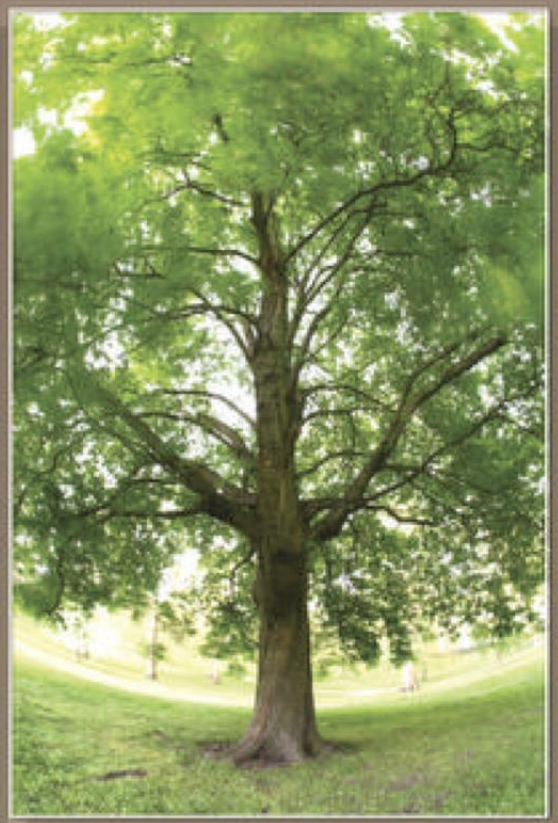
- *Mutation*
- *Sequence Change*
- *Protein Change*
- *Percentage Change*
- *Coverage*
- *Translocation*
- *Copy Number Variation/Amplification*

*Please note 34 genes listed, 35th gene under consideration/development

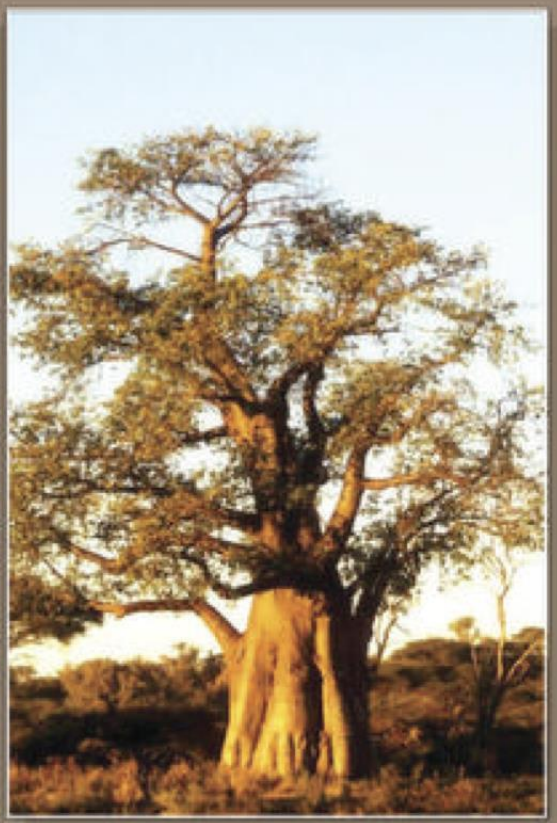
B

Clonal architecture as a biomarker

Palm tree



Chestnut tree



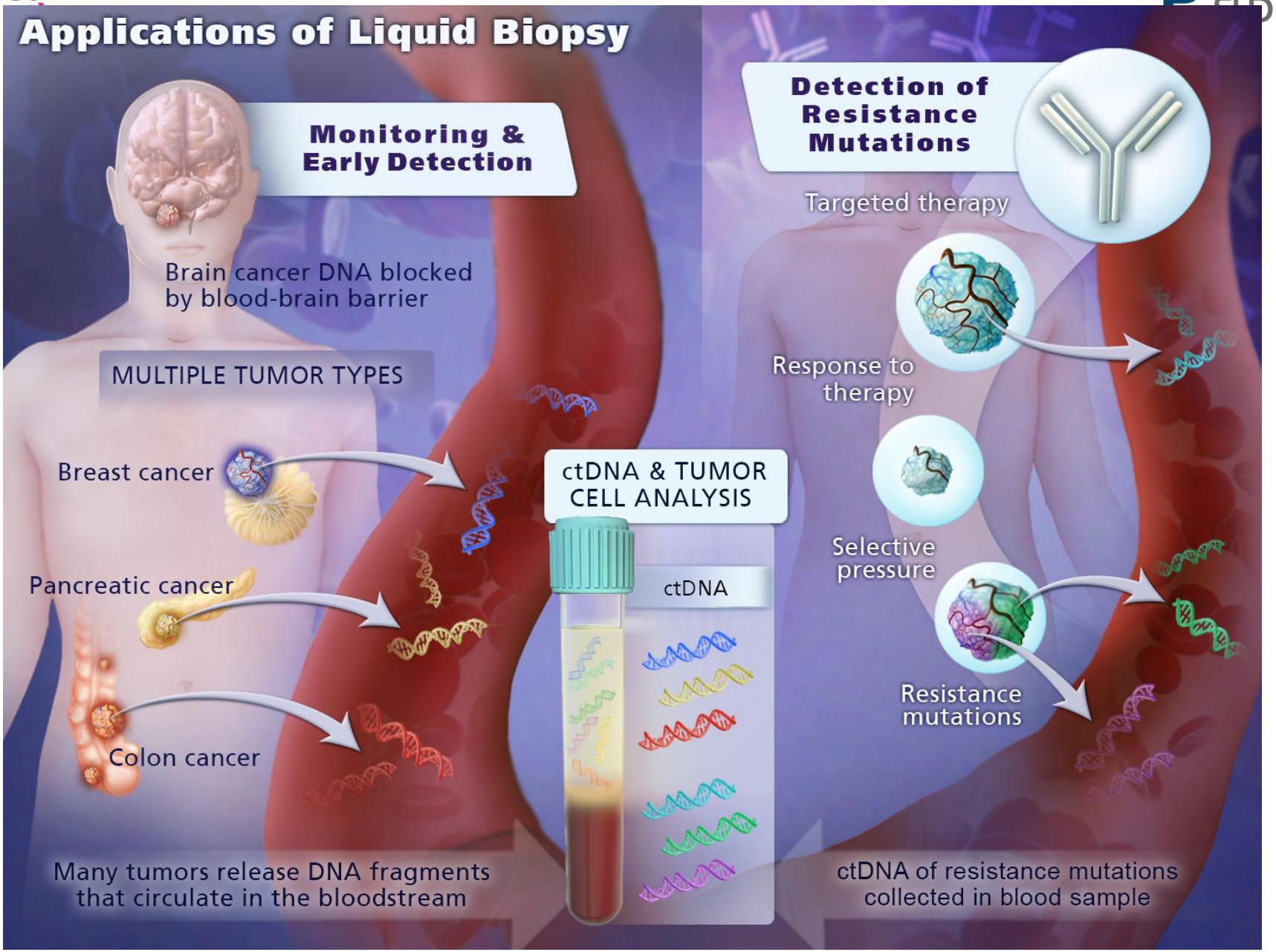
Baobab tree

Risk of treatment failure ?

Yap, Gerlinger, Pusztai, Futreal and Swanton Sci Trans Med 2012

Evolution of tumour molecular profiling in lung cancer

- Trials have moved from metastatic to resected disease
- Molecular read-outs have been enriched
- Access to targeted therapies is now encompassed in many designs
  - → Better collaboration with pharma companies
- The lastest generation of trials is randomizing against SOC
- Multiple challenges remain to be solved
- But technological opportunities are enormous…



Courtesy A Bardelli

Lung Cancer Patient in the near future

Lung nodule/metastases

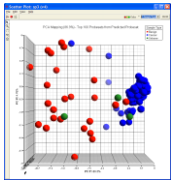
↓

Tumor Biopsy/ blood

↓

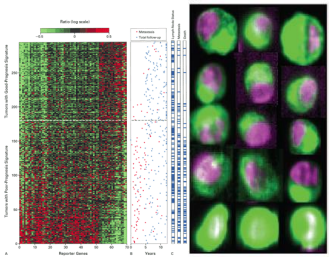
MOLECULAR PORTRAIT

Diagnostic



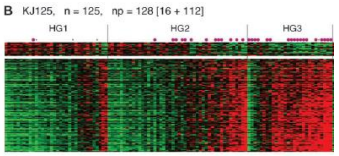
Cancer? Yes/No

Prognosis

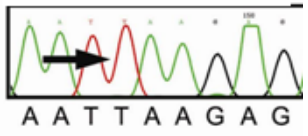


Need for treatment ?

Chemotherapy sensitivity



Targeted therapy sensitivity



Which treatment and when ?

Immunotherapy

PD1/PDL1
OX40
Other Pathways
…

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