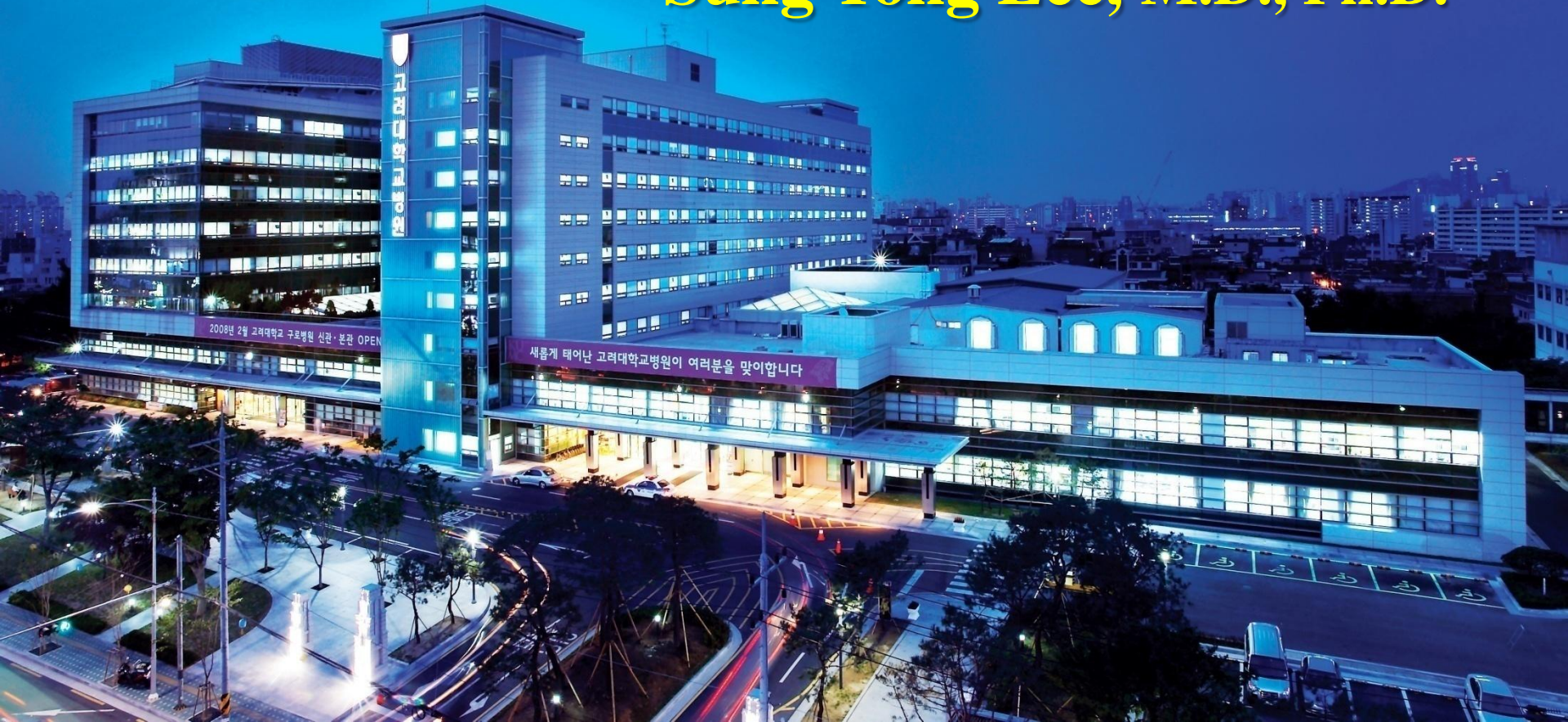


# Umbrella trials for lung cancer treatment

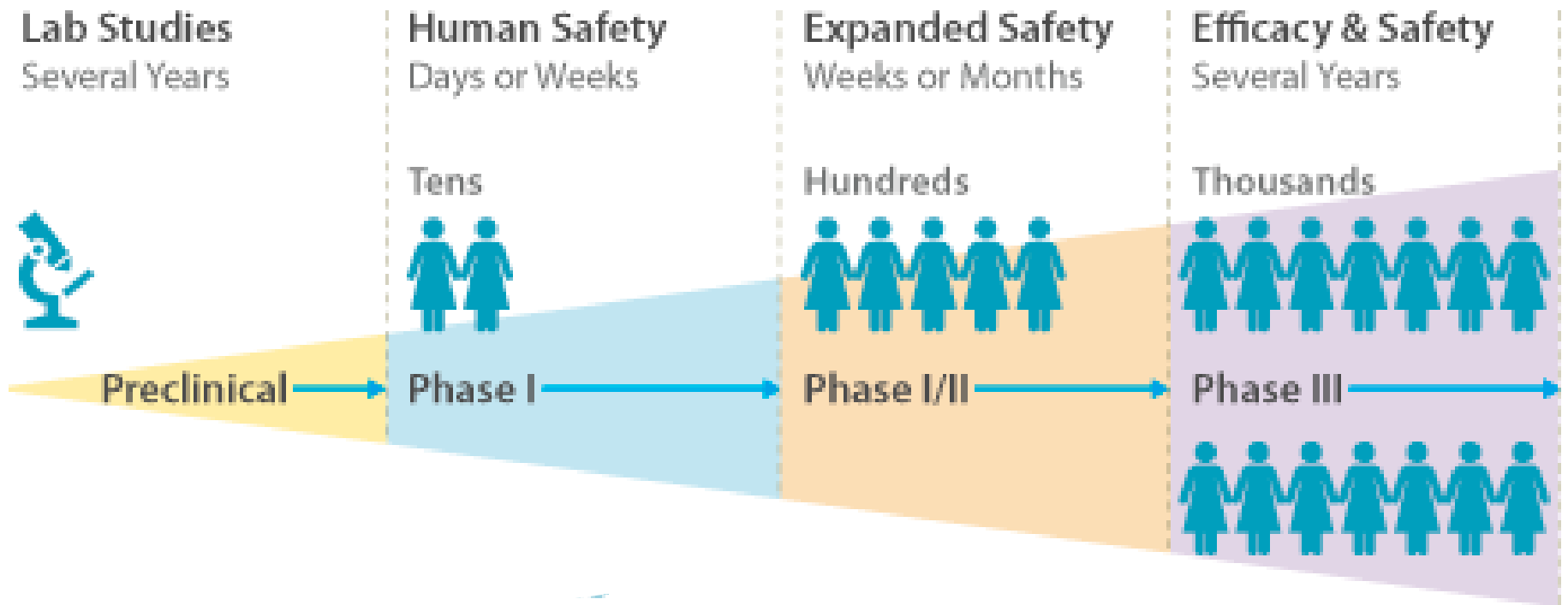
Korea University Medical Center

Department of Pulmonology and Critical Care Medicine

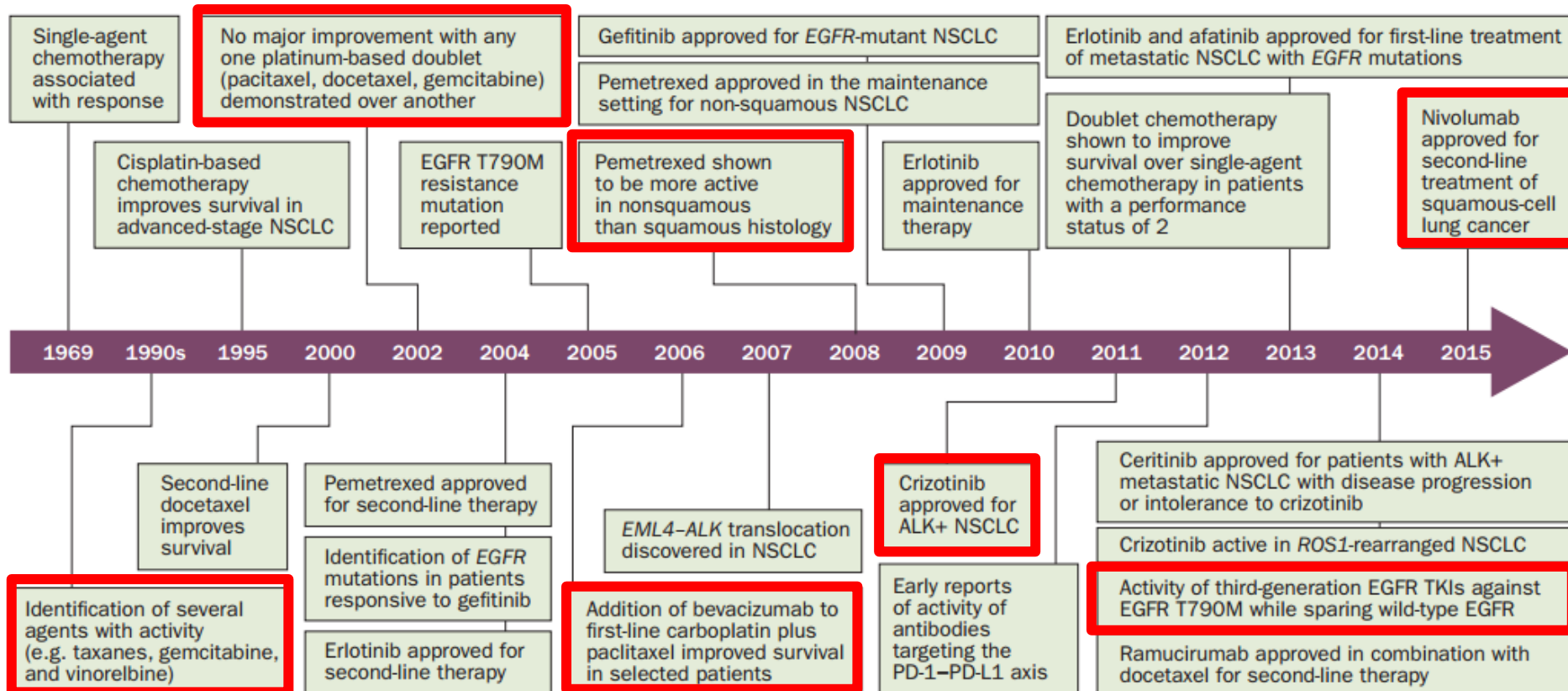
Sung Yong Lee, M.D., Ph.D.



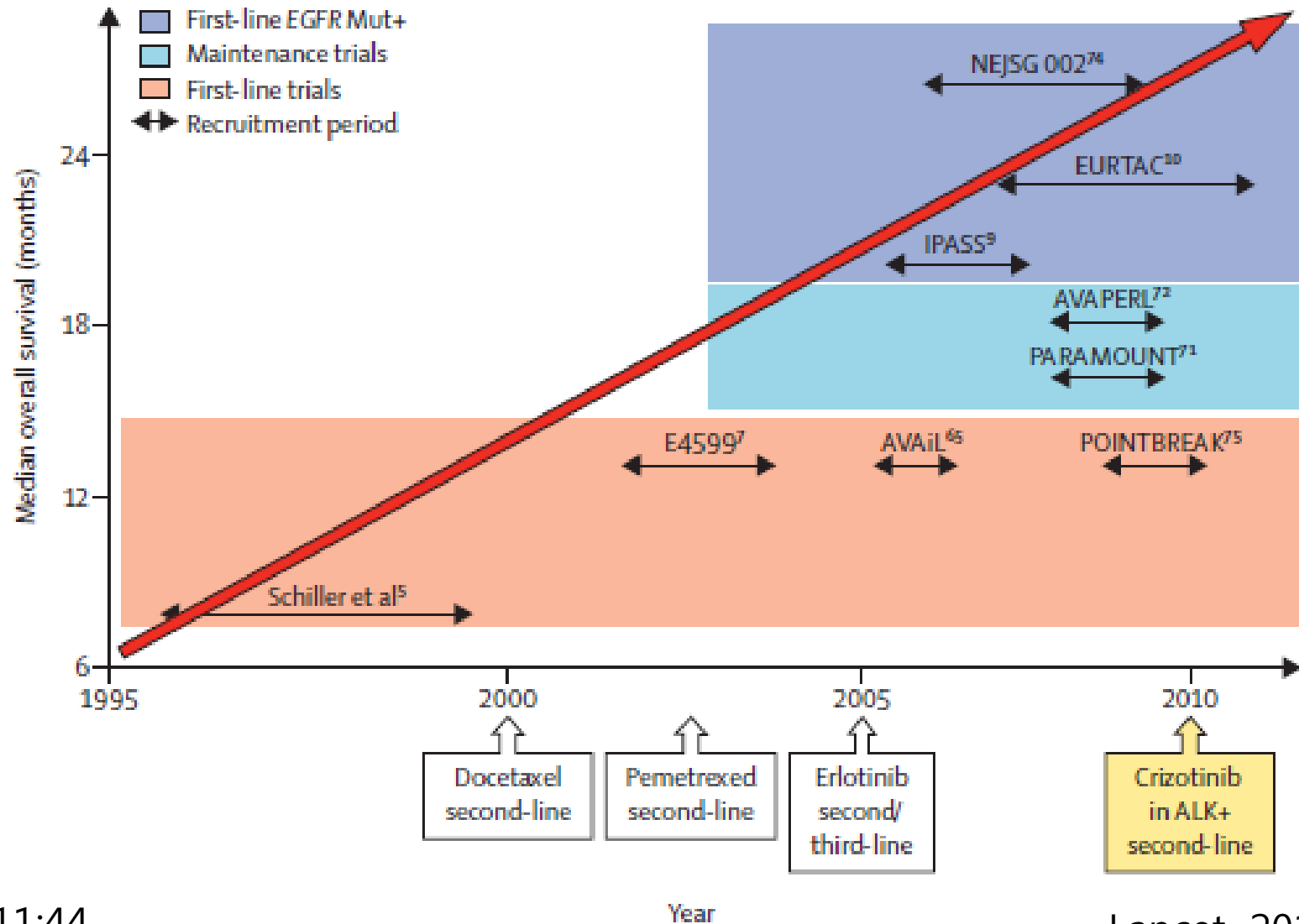
# Clinical Trial



# Historical milestones in NSCLC treatment



# Success History of NSCLC Treatment

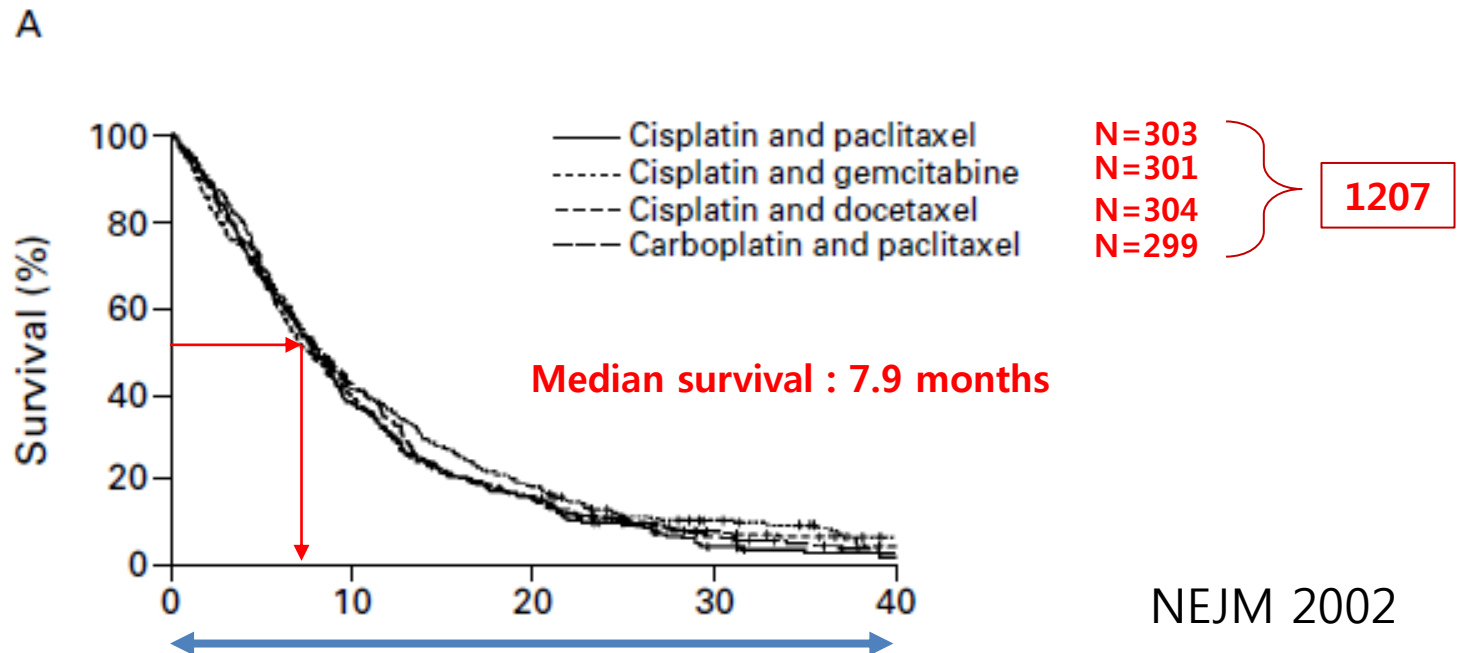


# Platinum-based doublet Treatment (ECOG1594)

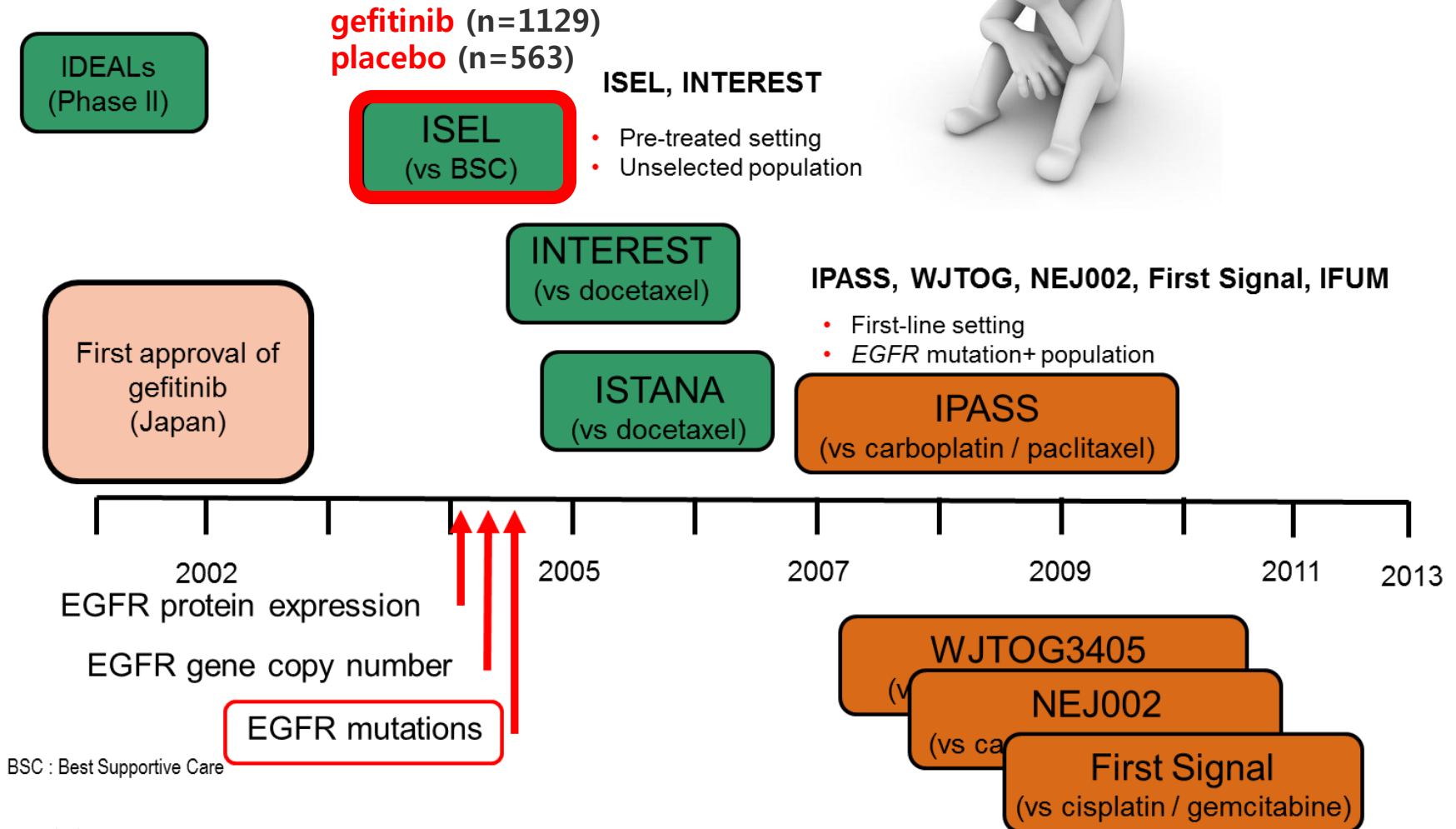
The New England Journal of Medicine

## COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON-SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D.,  
ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D.,  
FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

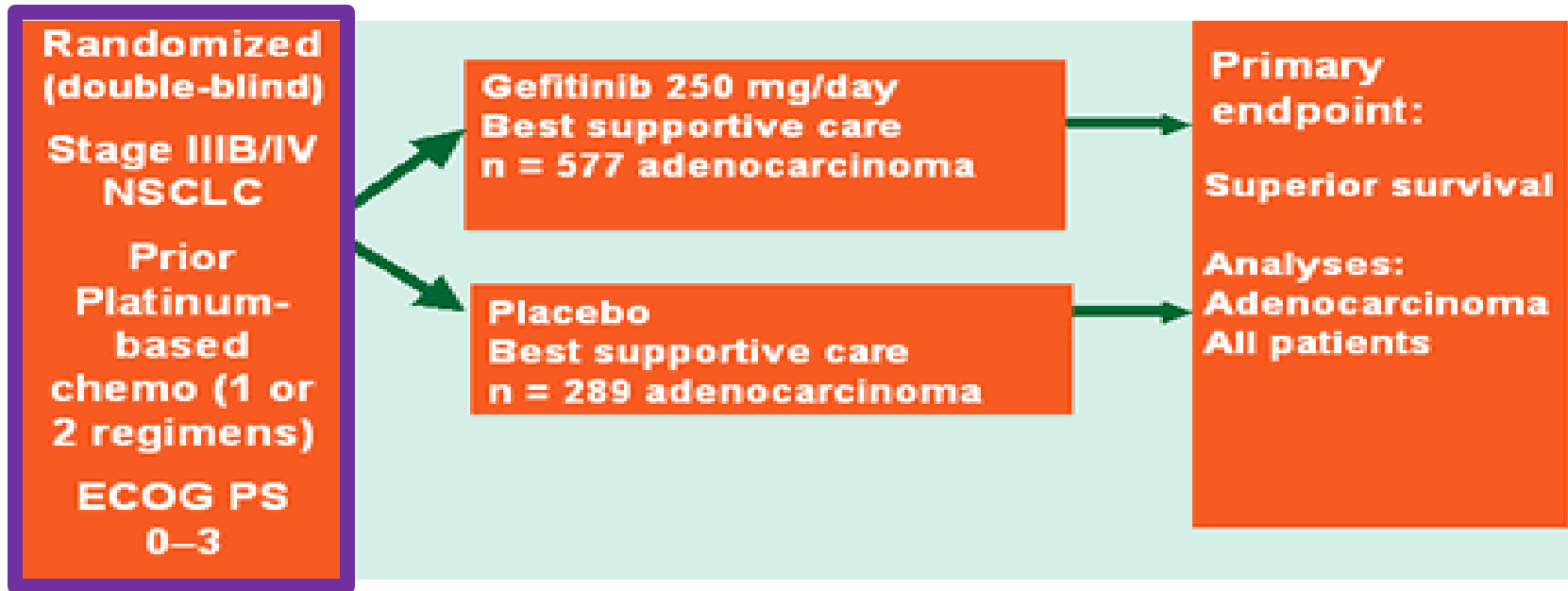


# Success story of Gefitinib



# ISEL

(Gefitinib Survival Evaluation in Lung Cancer)



**N=1692 patients**

Median survival overall: 5.6 vs. 5.1 months,  $p=0.11$

Median survival of adenocarcinoma: 6.3 vs. 5.4 mon,  $p=0.07$

Statistically significant response rate

**Asians and nonsmokers seem to benefit**



# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 20, 2004

VOL. 350 NO.

## Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordani, Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

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

J. Guillermo Paez, 1,2\* Pasi A. Jänne, 1,2\* Jeffrey C. Lee, 1,3\* Sean Tracy, 1 Heidi Greulich, 1,2 Stacey Gabriel, 4 Paula Herman, 1 Frederic J. Kaye, 5 Neal Lindeman, 6 Titus J. Boggon, 1,3 Katsuhiko Naoki, 1 Hidefumi Sasaki, 7 Yoshitaka Fujii, 7 Michael J. Eck, 1,3 William R. Sellers, 1,2,4\* Bruce E. Johnson, 1,2 Matthew Meyerson, 1,3,4\* Departments of Medical Oncology and Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115 USA, 3Department of Pathology and Biological Chemistry and Harvard Medical School, Boston, MA 02115 USA, 4The Broad Institute at MIT and Harvard, Cambridge, MA 02142, USA, 5Genetics Branch, National Cancer Institute, National Naval Medical Center, Bethesda, MD 20889, USA, 6Department of Pathology, Brigham and Women's Hospital, Boston MA 02115, USA, 7Department of Surgery 2, Nagoya City University Medical School, Nagoya 467-8601, Japan.

## ScienceExpress

Report

# EGFR Mutation and EGFR TKIs

# IPASS: Molecular Oncology Overrides Clinical Features

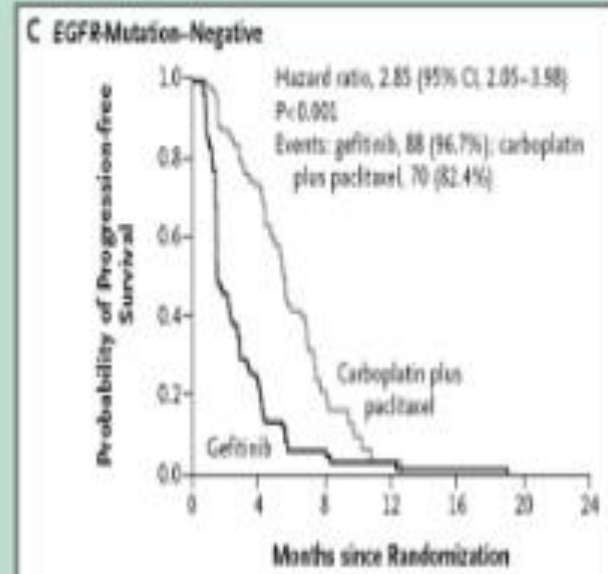
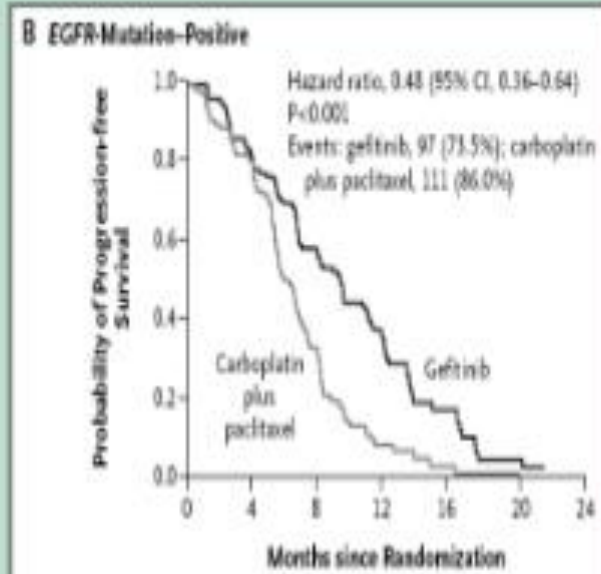
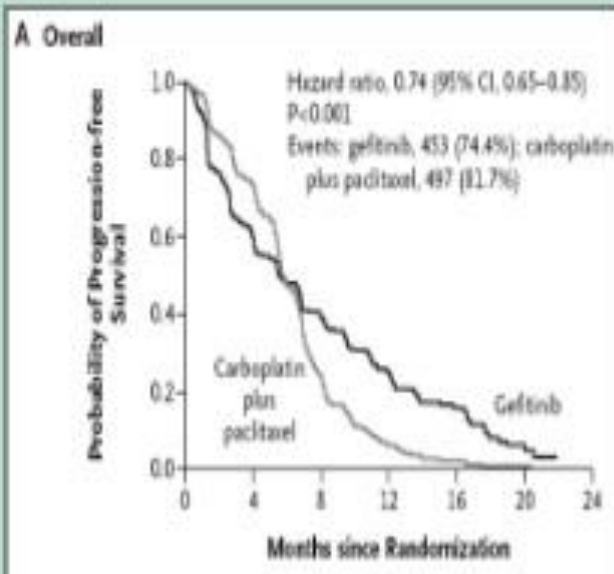
advanced lung adenocarcinoma,  
Asian  
no prior systemic Rx  
Never or light ex-smoker



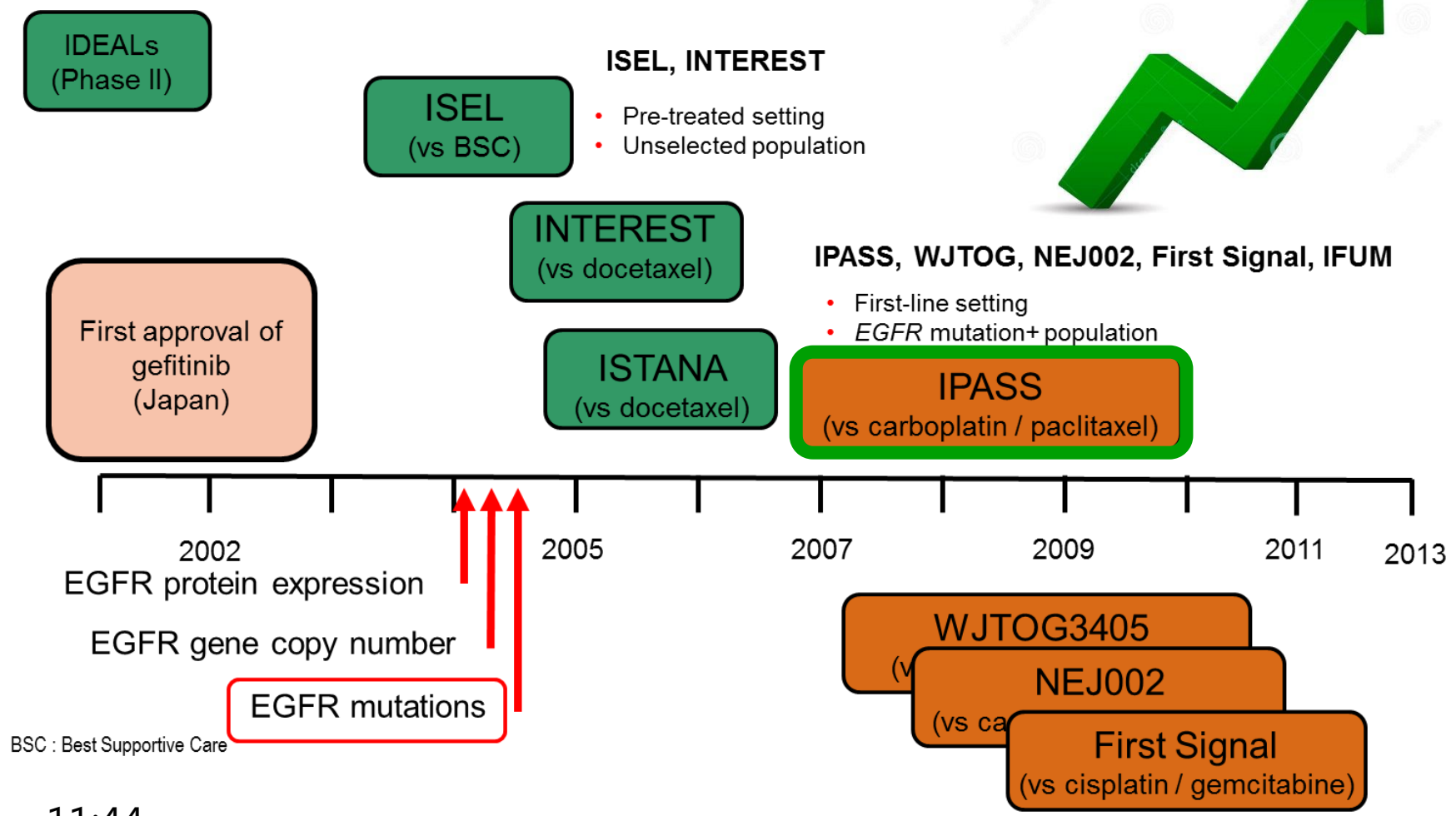
Carbo/paclitaxel x 6 cycles



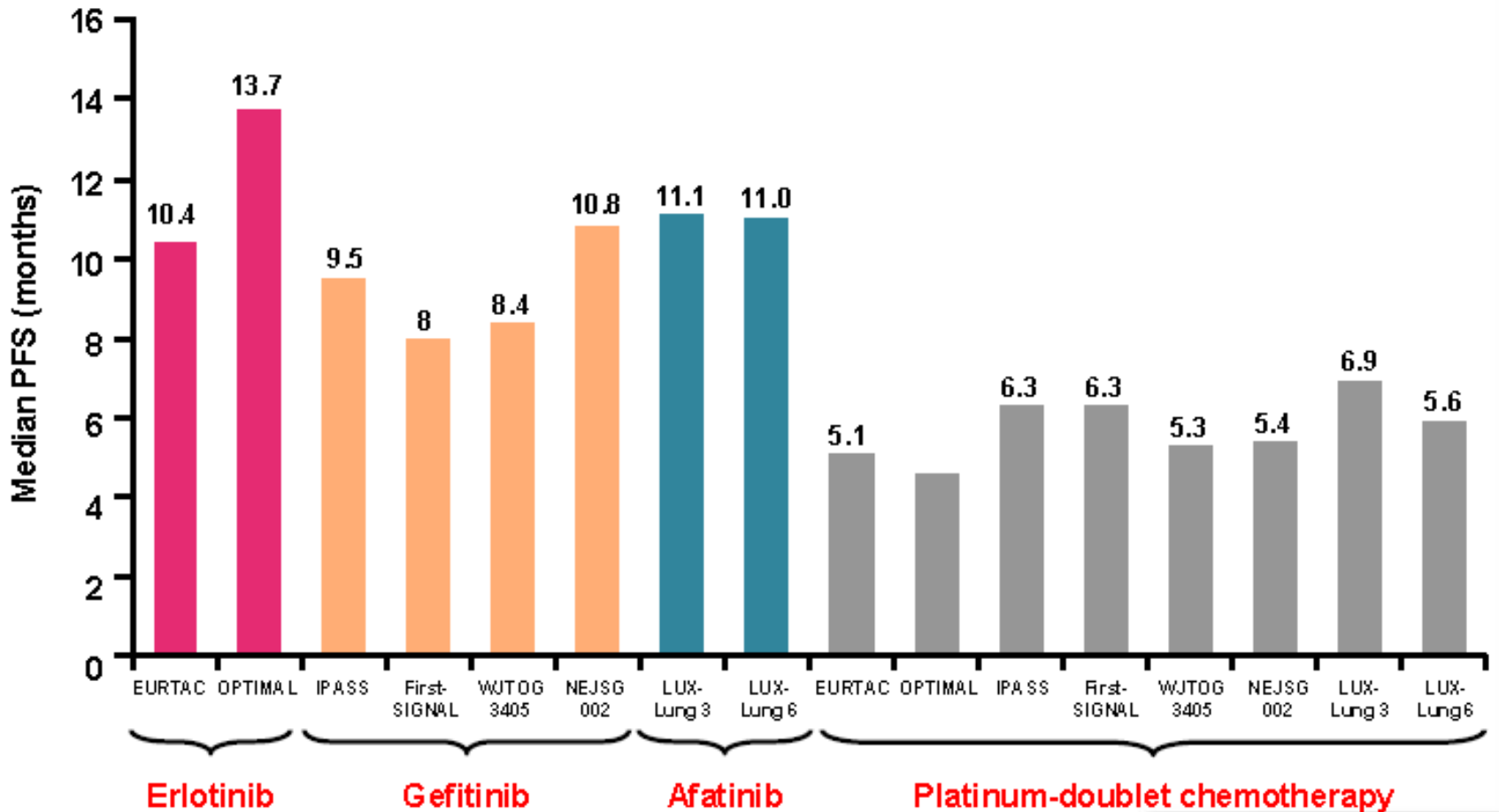
Gefitinib daily until progression



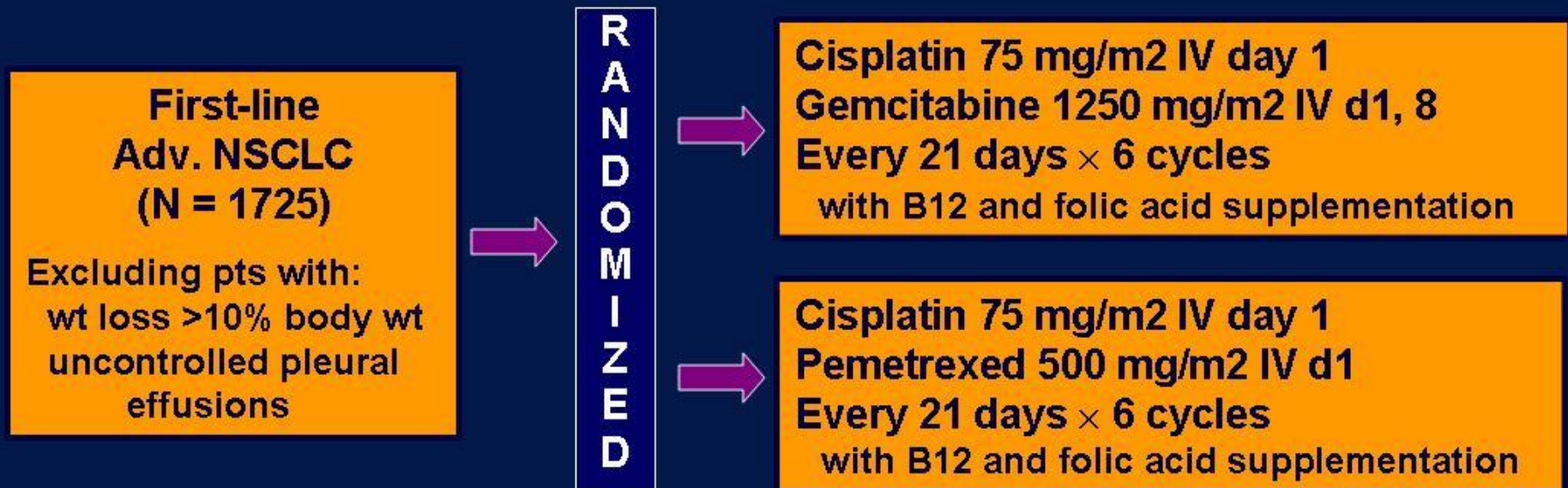
# A success story of gefitinib



# Median PFS in First-line phase III Trials EGFR M(+) patients

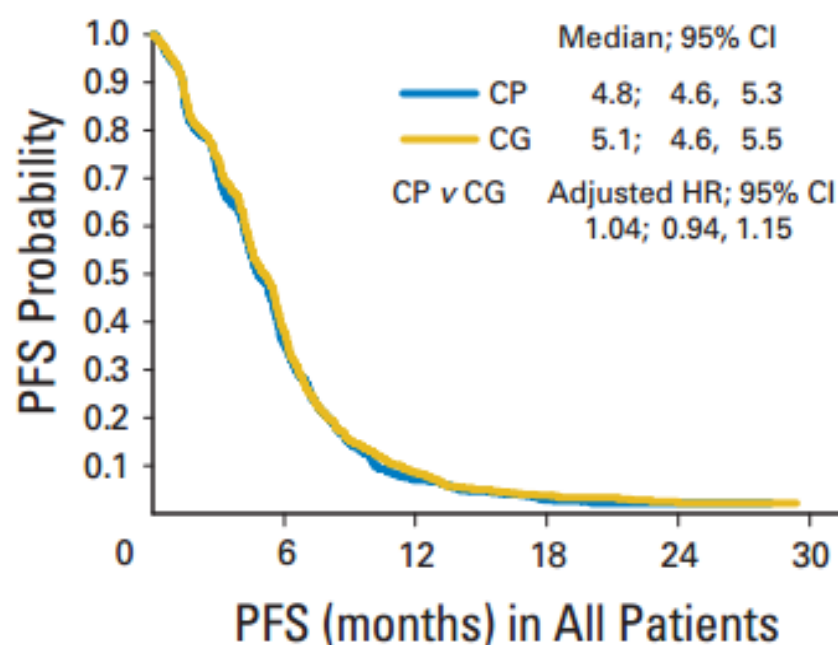
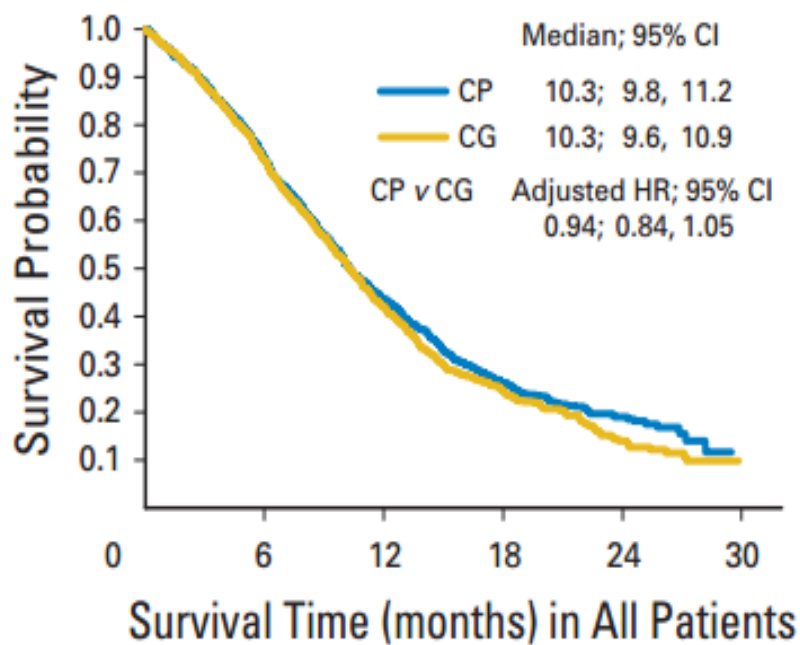


# “JMDB” Randomized Phase III Trial of Cisplatin/Gemcitabine vs. Cisplatin/Alimta



- **Primary endpoint: Overall Survival**
- **Pre-specified/planned analysis of results by tumor histology**

# JMDB (Cis/Alimta vs. Cis/Gemcitabine as First Line Therapy for Adv. NSCLC): Survival by Histology



# 고전적 임상시험

- ✓ 천명 이상의 피험자들을 대상으로 하여 몇 가지 수치를 측정
- ✓ 대상자들을 두 그룹으로 나눈다(control vs. case)
- ✓ 약효를 검증하고 그 메커니즘 검증을 위한 후속연구 필요

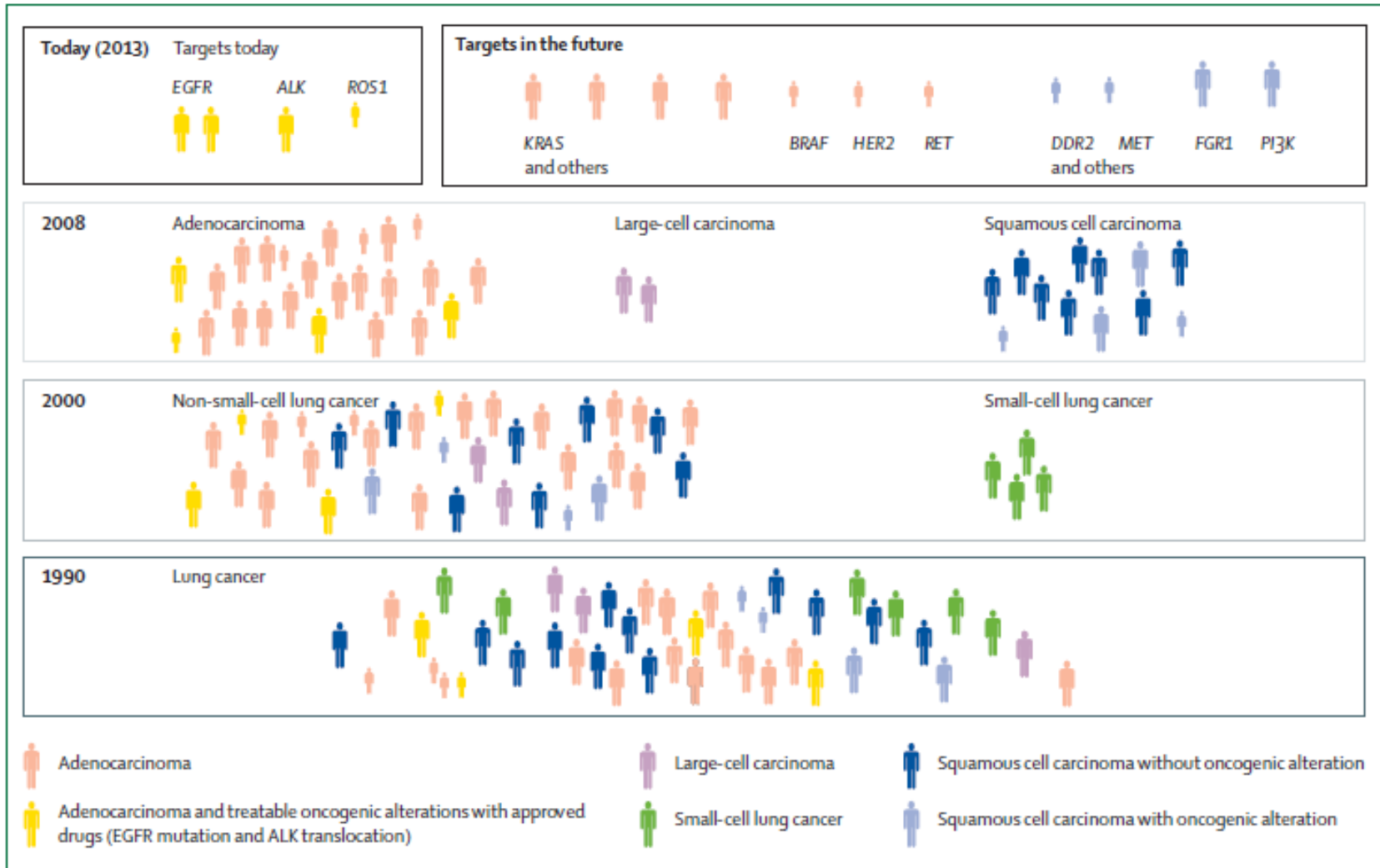
**“trials designed to learn”**



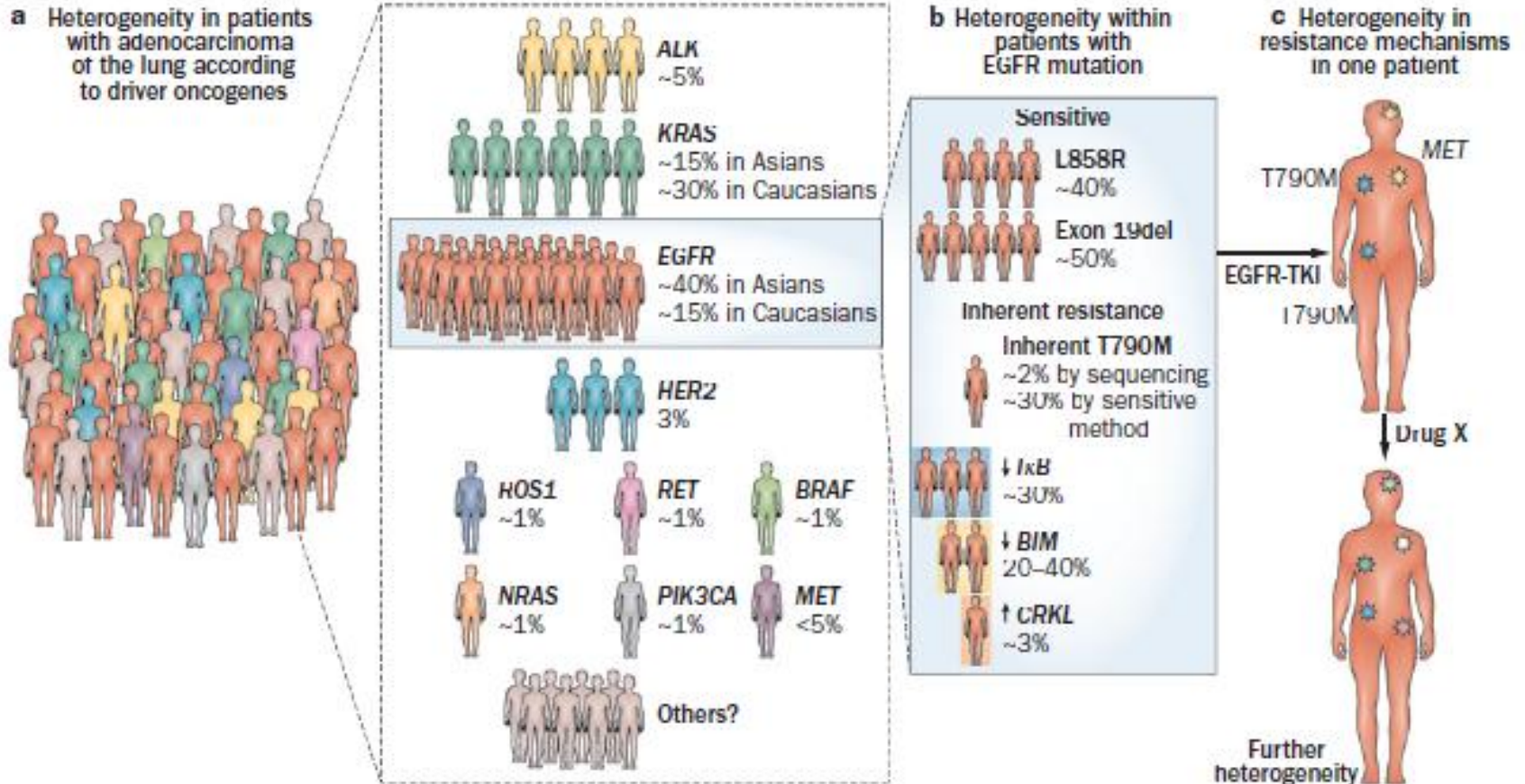


NEW IDEAS. NEW REALITY.  
**NEW PARADIGM.**

# Heterogeneity of NSCLC: inter-individual



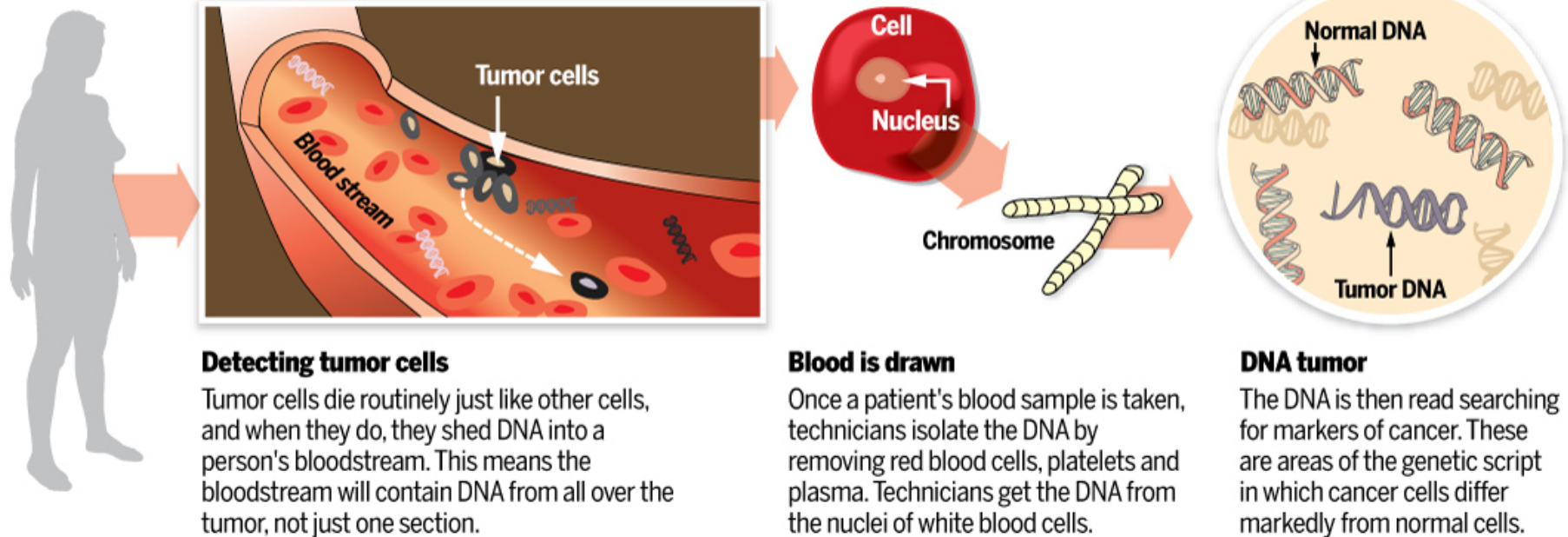
# Molecular Heterogeneity of NSCLC : intra-individual



# New Developments of Diagnostic Methods in Lung Cancer

## How 'liquid biopsies' work

Different sections of a tumor have different genetic scripts. Taking a biopsy from the tumor itself will tell you only about the DNA in one part of the tumor.



### Detecting tumor cells

Tumor cells die routinely just like other cells, and when they do, they shed DNA into a person's bloodstream. This means the bloodstream will contain DNA from all over the tumor, not just one section.

### Blood is drawn

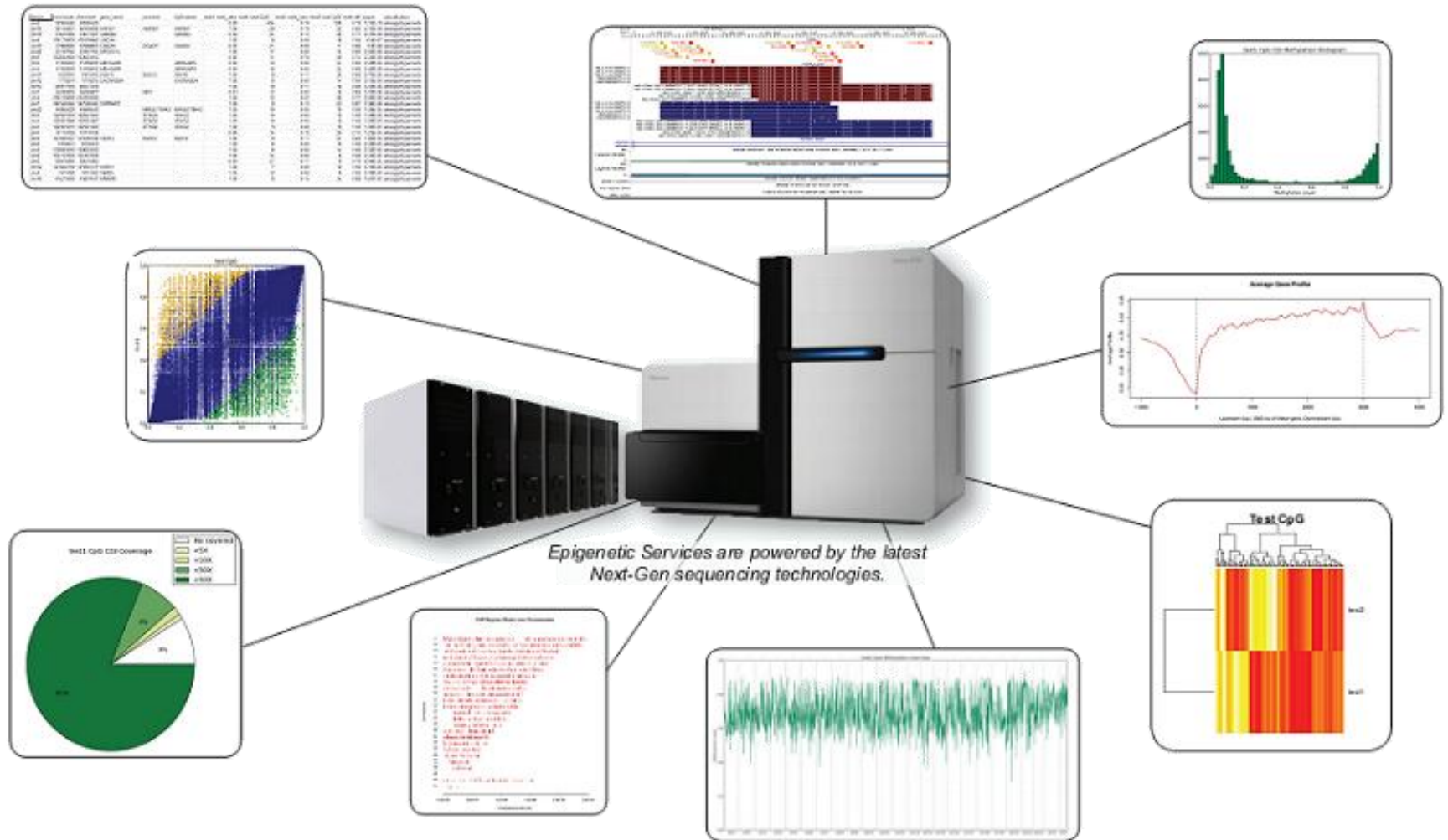
Once a patient's blood sample is taken, technicians isolate the DNA by removing red blood cells, platelets and plasma. Technicians get the DNA from the nuclei of white blood cells.

### DNA tumor

The DNA is then read searching for markers of cancer. These are areas of the genetic script in which cancer cells differ markedly from normal cells.

# New Developments of Diagnostic Methods in Lung Cancer

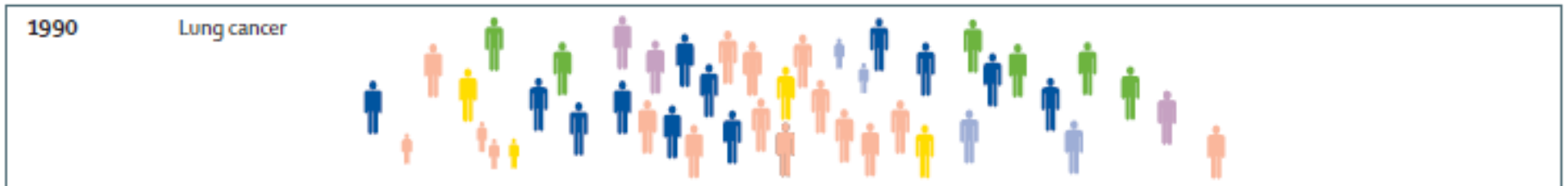
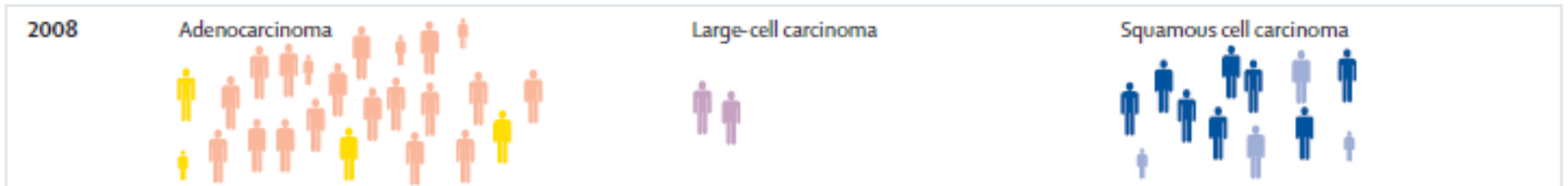
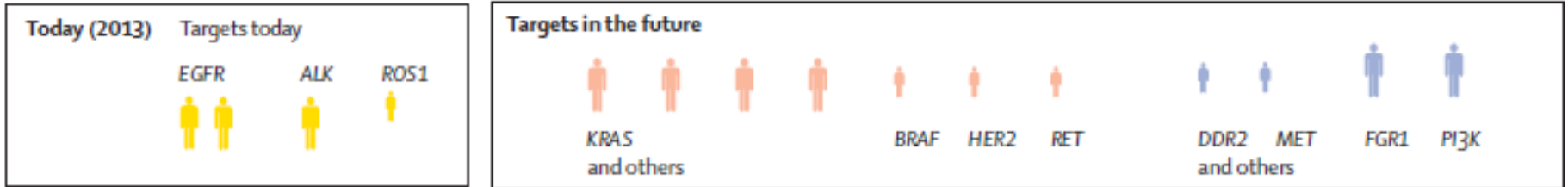
## Genotype-directed targeted therapies



# 분자생물학적 표적 vs. 표적치료제

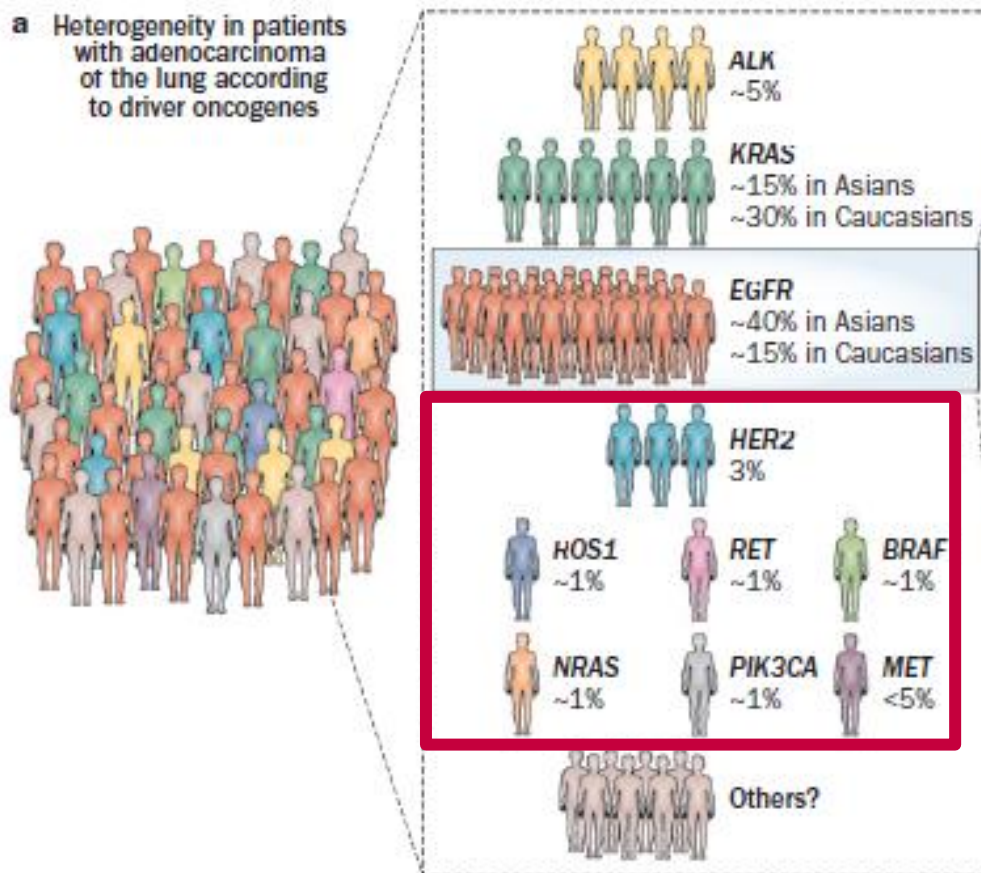
Biomarker gene	Aberration	Targeted therapeutic
<i>EGFR</i>	Mutation or amplification	Gefitinib, erlotinib, cetuximab
<i>HER2 (ERBB2)</i>	Mutation or amplification	Trastuzumab
<i>BRAF</i>	Mutation	Sorafenib
<i>p53</i>	Mutation or deletion	Advexin a p53 adenoviral vector
<i>VEGF</i>	Overexpression	Bevacizumab, afibercept
<i>PI3K</i>	Modified and activated	BEZ235, LY294002
<i>mTOR</i>	Activated	Rapamycin, RAD001, CCL-779
<i>RAS</i>	Mutation leading to activation	Tipifarnib, lonafarnib
<i>MEK</i>	Activated	Trametinib, salumetinib
<i>c-KIT</i>	Overexpressed	Imatinib
<i>EML/ALK</i>	Fusion	Crizotinib

# 표적치료 → 맞춤치료

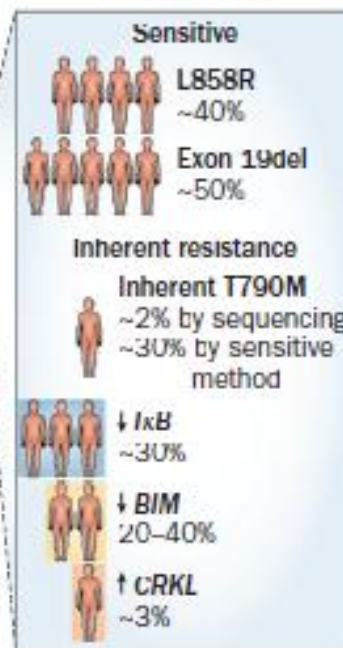


# 맞춤치료와 임상연구

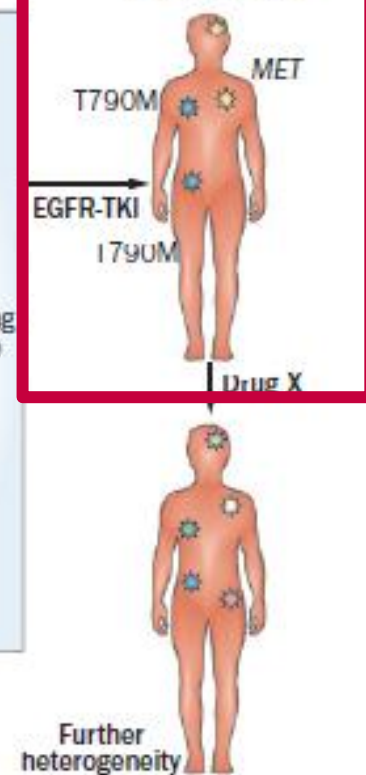
**a** Heterogeneity in patients with adenocarcinoma of the lung according to driver oncogenes



**b** Heterogeneity within patients with EGFR mutation

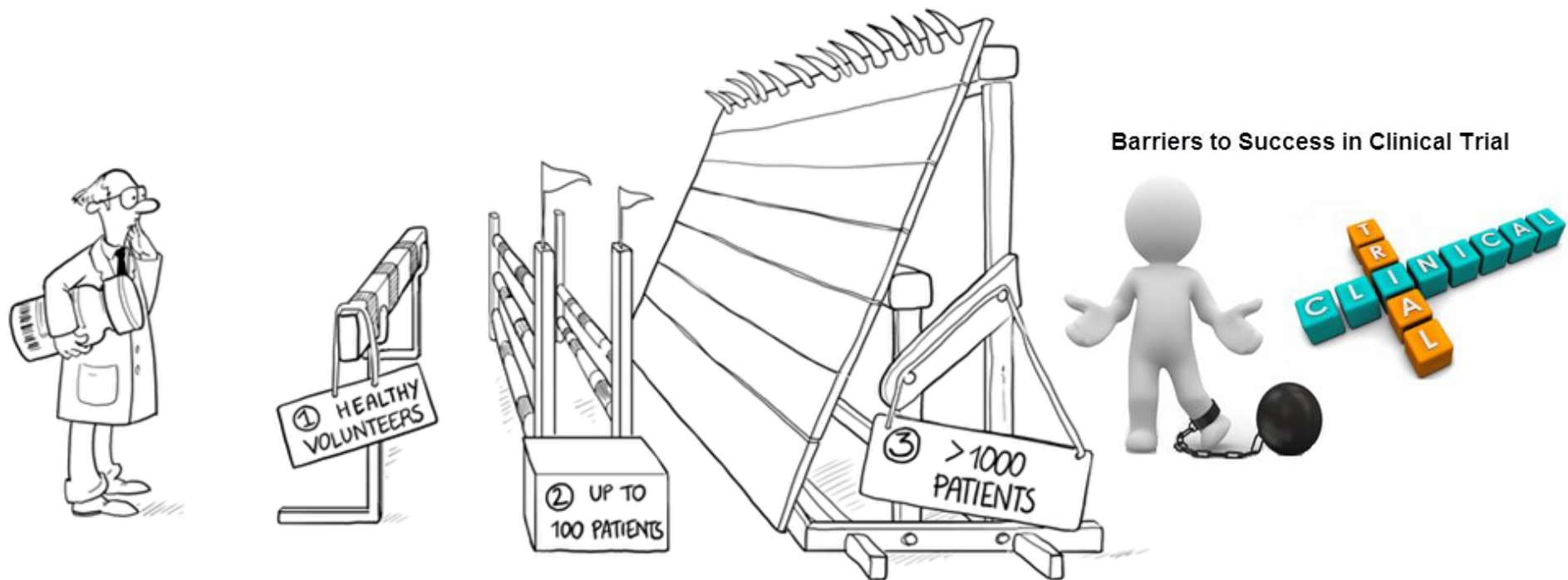


**c** Heterogeneity in resistance mechanisms in one patient



# Conventional Clinical Trials

**~7.6 years for oncologic compounds**



# 맞춤의료 (Personalized Medicine) 시대의 임상시험의 문제점

- ✓ 표적치료제는 그 유효성이 모든 환자에게서 동일하게 나타나지 않음
- ✓ 과거 특정 질병에 대해 **획일적인 치료방법**이 적용되었으나, 최근에는 분자생물학적 진단의 개발로 개인의 **유전적 특성**에 따른 맞춤치료가 이루어짐.
- ✓ **소수의 환자들에서 발현**하는 유전자를 표적으로하는 임상시험의 경우 기존의 임상시험으로는 **시간, 돈, 인력의 문제점**들이 발생함 (screening failure rate가 높다).

- ✓ **Understanding the molecular biology of cancer**
- ✓ **Innovations in drug development technology**
- ✓ **Translation of these findings into effective cancer treatment**

# **New era of new clinical trials**

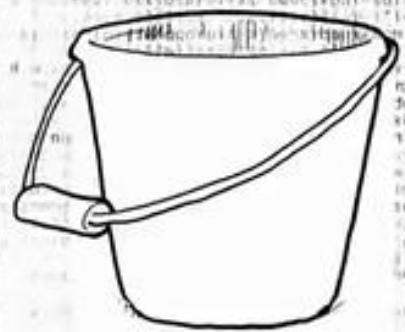


# New era of new clinical trials

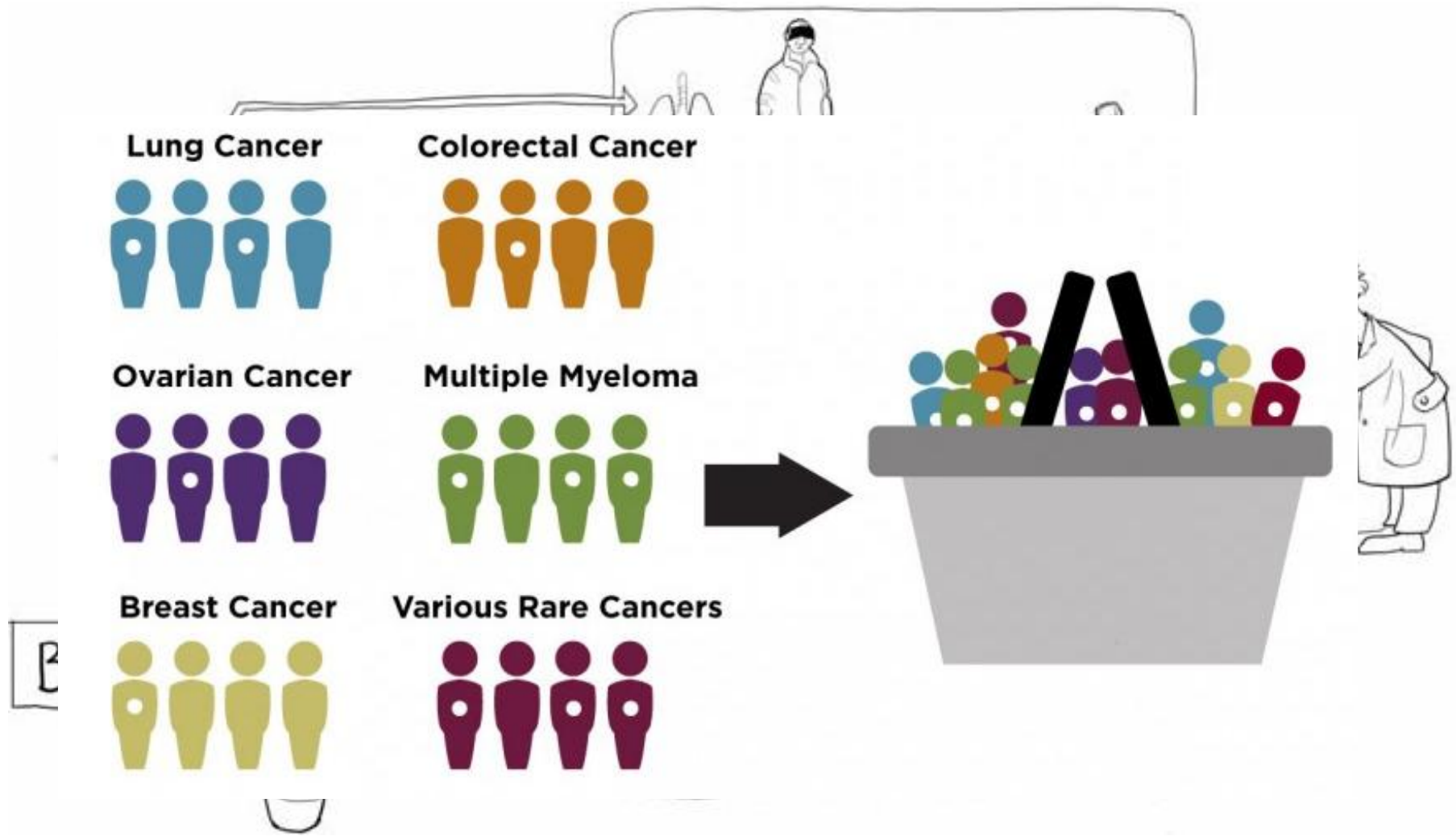
UMBRELLA TRIAL



BUCKET TRIAL  
(OR BASKET)



# Basket Trial ; **One drug** - multiple disease



# Basket Trial ; **One drug** - multiple disease

8 cohorts  $BRAF^{V600}$  positive cancers:

Metastatic solid tumors

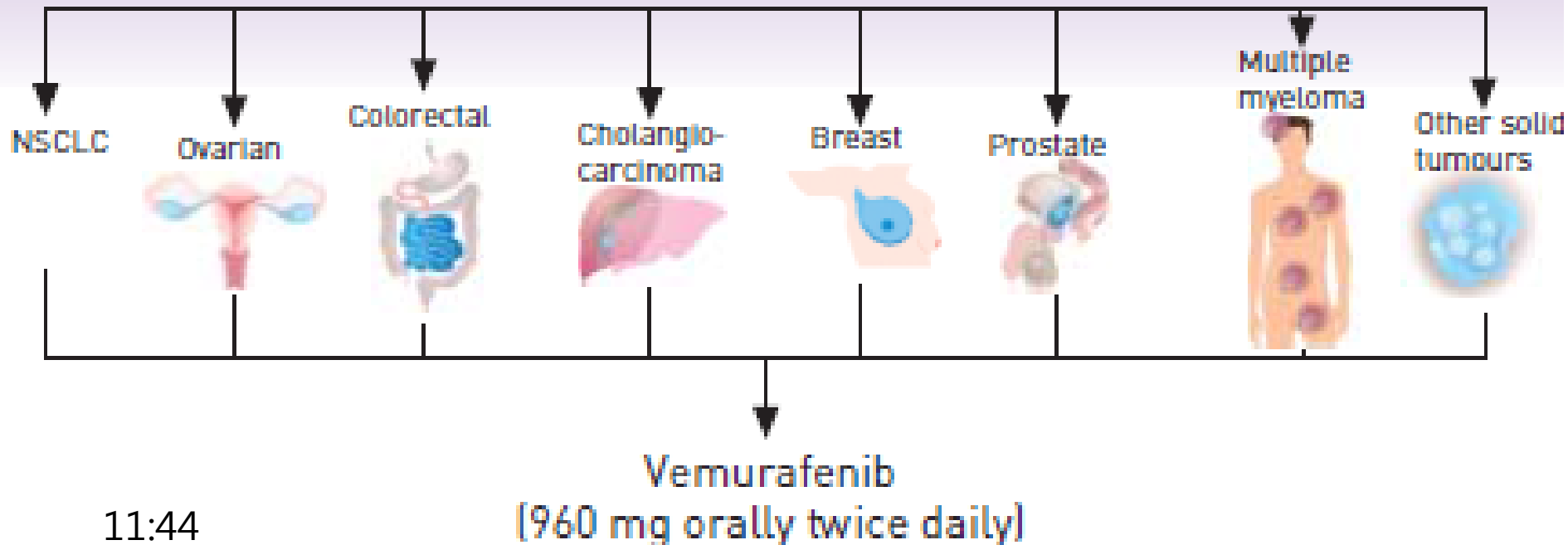
Multiple myeloma

$BRAF^{V600}$  testing

All  $BRAF^{V600}$  mutations

Tested by local routine methods

Retrospective optional evaluation with cobas 4800  $BRAF$  mutation test



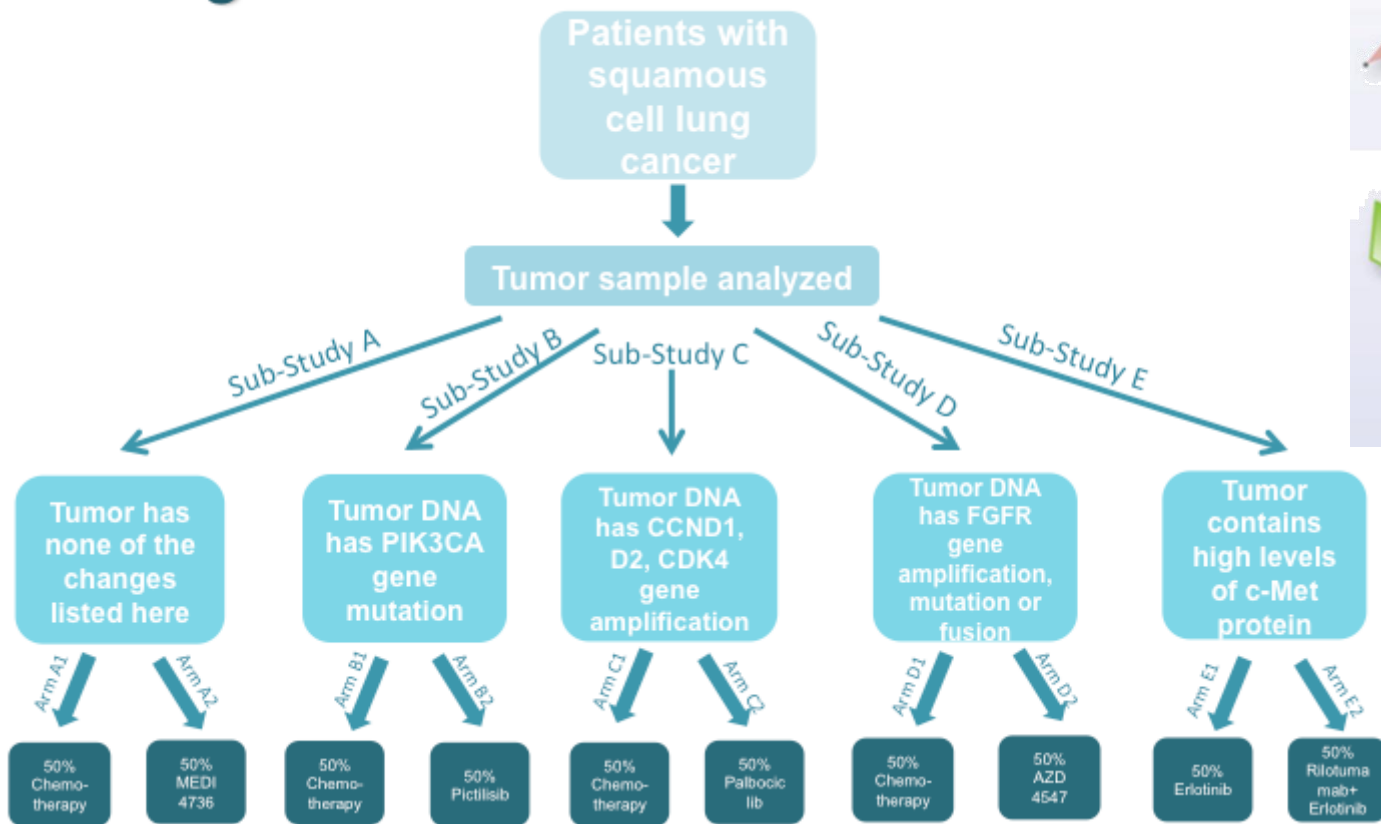
# Umbrella Trial; One disease - Multiple drugs



# Umbrella Trial

하나의 질병에 대해 여러 가지 약물의 효능을 테스트하는 임상

## Lung-MAP Sub-Studies for Treatment





# Umbrella Trial의 실제

# Ongoing Umbrella Trials

Trial	Biomarker-driven	Disease setting	Design	Design type
<b>ALCHEMIST</b>	Yes	<b>Adjuvant</b> non-squamous NSCLC	Phase 3	Confirmatory
<b>FOCUS 4</b>	Yes	Advanced colon	Phase 2 followed by phase 3	Discovery and confirmatory
<b>I-SPY2</b>	No	Neo-adjuvant breast	Phase 2	Discovery
<b>BATTLE</b>	Yes	<b>Recurrent</b> NSCLC	Phase 2	Discovery
<b>Lung-MAP</b>	Yes	Previously treated <b>squamous lung cancer</b>	Phase 2/3	Confirmatory
<b>National Lung MATRIX trial</b>	Yes	<b>NSCLC</b>	Single-arm phase 2	Discovery

**“BATTLE” as a Novel Approach in 2004**

***Biomarker-Integrated Approaches of Targeted  
Therapy for Lung Cancer Elimination***

**“폐암퇴치를 위한 바이오마커에 근거한 표적치료 임상”**

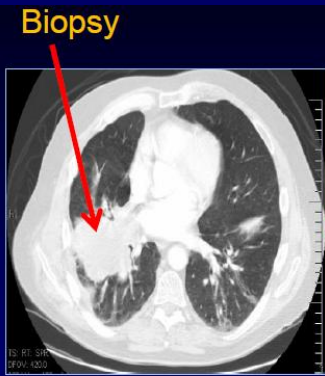
# Enrollment into BATTLE-1 Umbrella Protocol

Activated

Eligibility

Prior chemotherapy

Biopsiable disease



**Core Biopsy**

## Biomarker Assessment

1. EGFR mutation
2. EGFR Increased copy number
3. KRAS mutation
4. BRAF mutation
5. VEGF expression
6. VEGFR-2 expression
7. RXRa expression
8. RXRb expression
9. RXRg expression
10. Cyclin D1 expression
11. Cyclin D1 amplification



## Biomarker Profile and Adaptive Randomization

EGFR

Ras/Raf

VEGF

CycD1/RXR

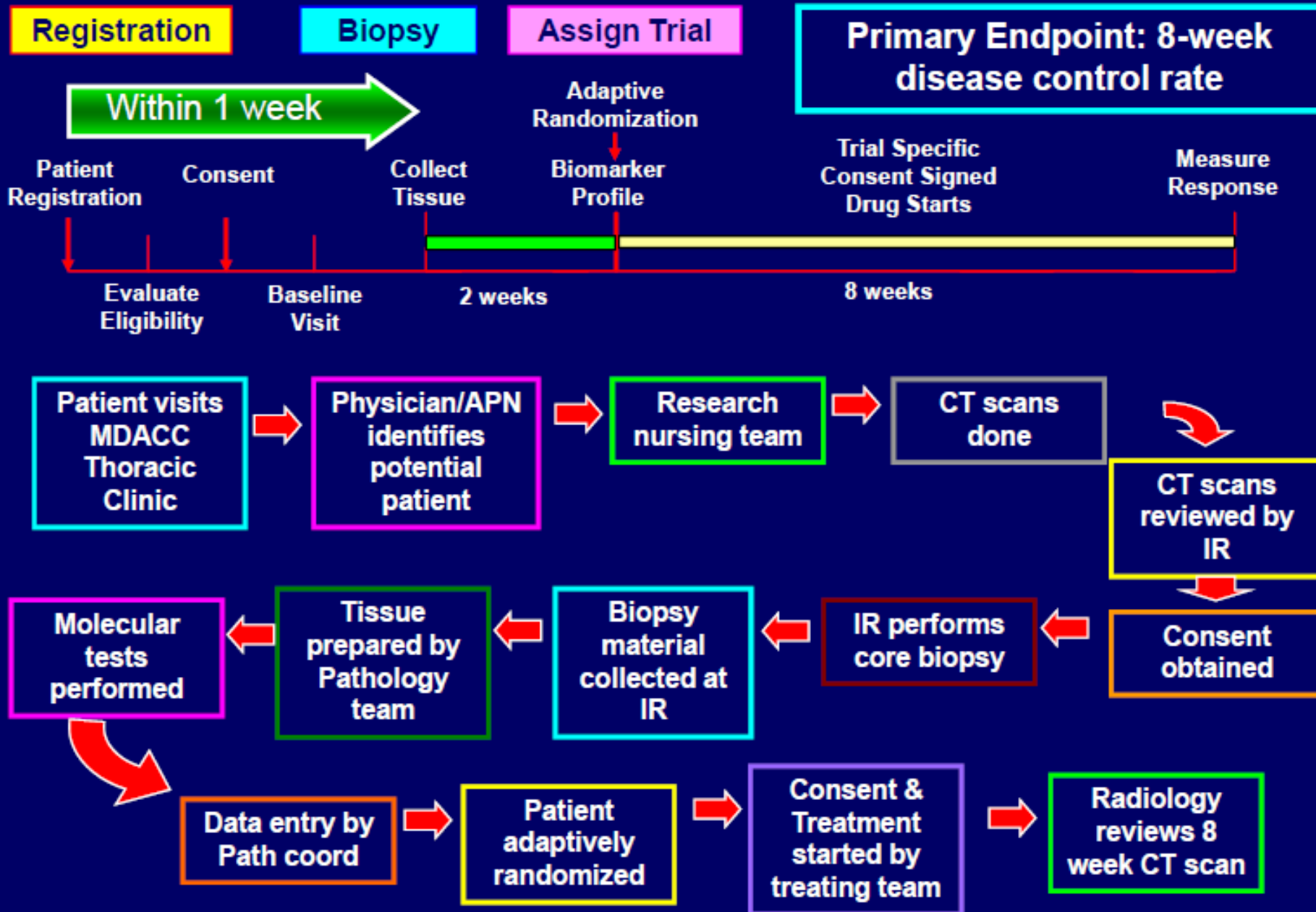
Erlotinib

Sorafenib

Vandetanib

Erlotinib + Bexarotene

# BATTLE-1 Workflow



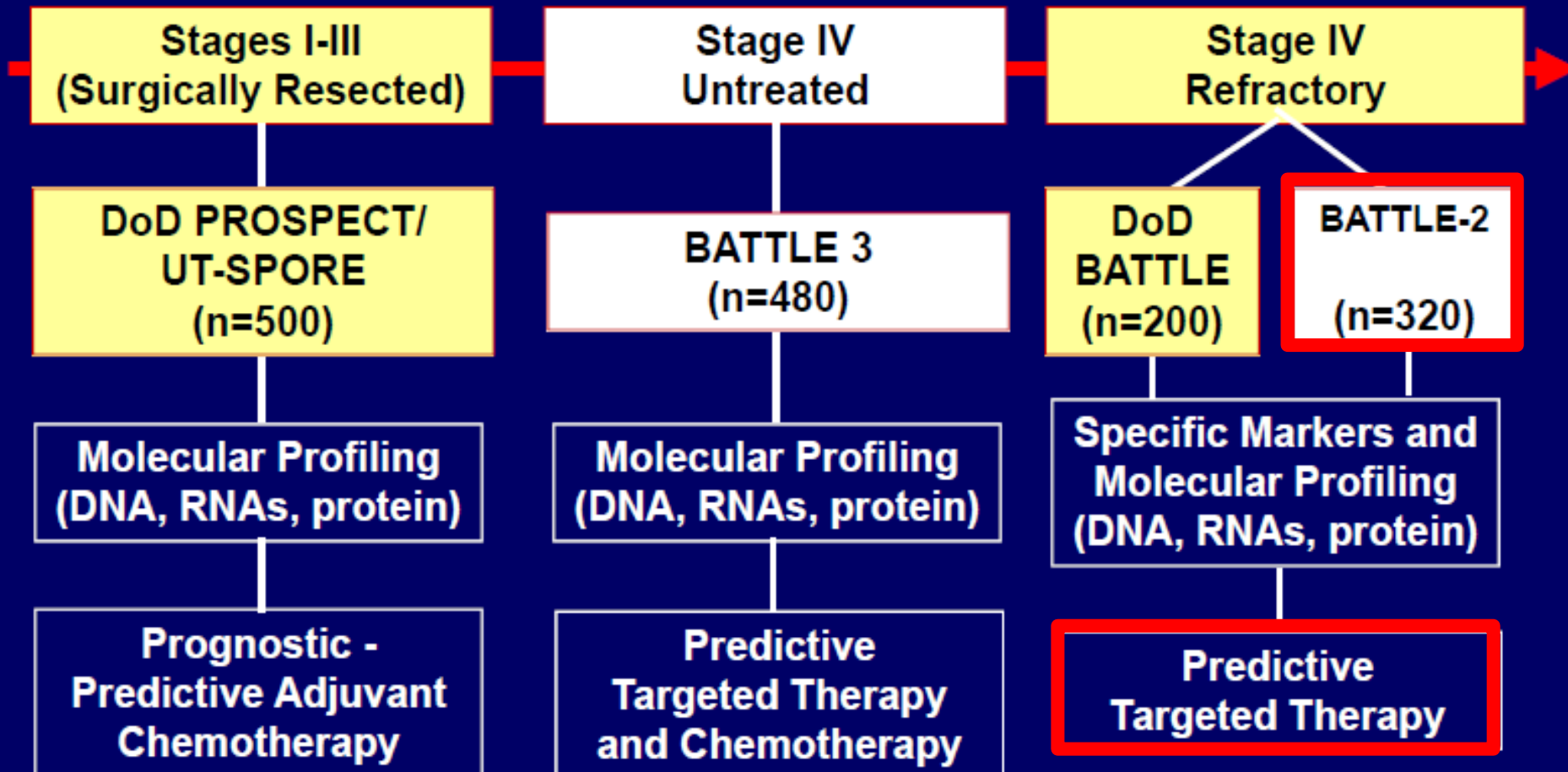
# BATTLE Results: Disease Control in % (n)

	Marker Groups					Total
	<i>EGFR</i>	<i>KRAS</i>	VEGF	RXR/ CycD1	None	
Erlotinib	35% (17)	14% (7)	40% (25)	0% (1)	38% (8)	34% (58)
Vandetanib	41% (27)	0% (3)	38% (16)	NA (0)	0% (6)	33% (52)
Erlotinib + Bexarotene	55% (20)	33% (3)	0% (3)	100% (1)	56% (9)	50% (36)
Sorafenib	39% (23)	79% (14)	64% (39)	25% (4)	61% (18)	58% (98)
Total	43% (87)	48% (27)	49% (83)	33% (6)	46% (41)	46% (244)

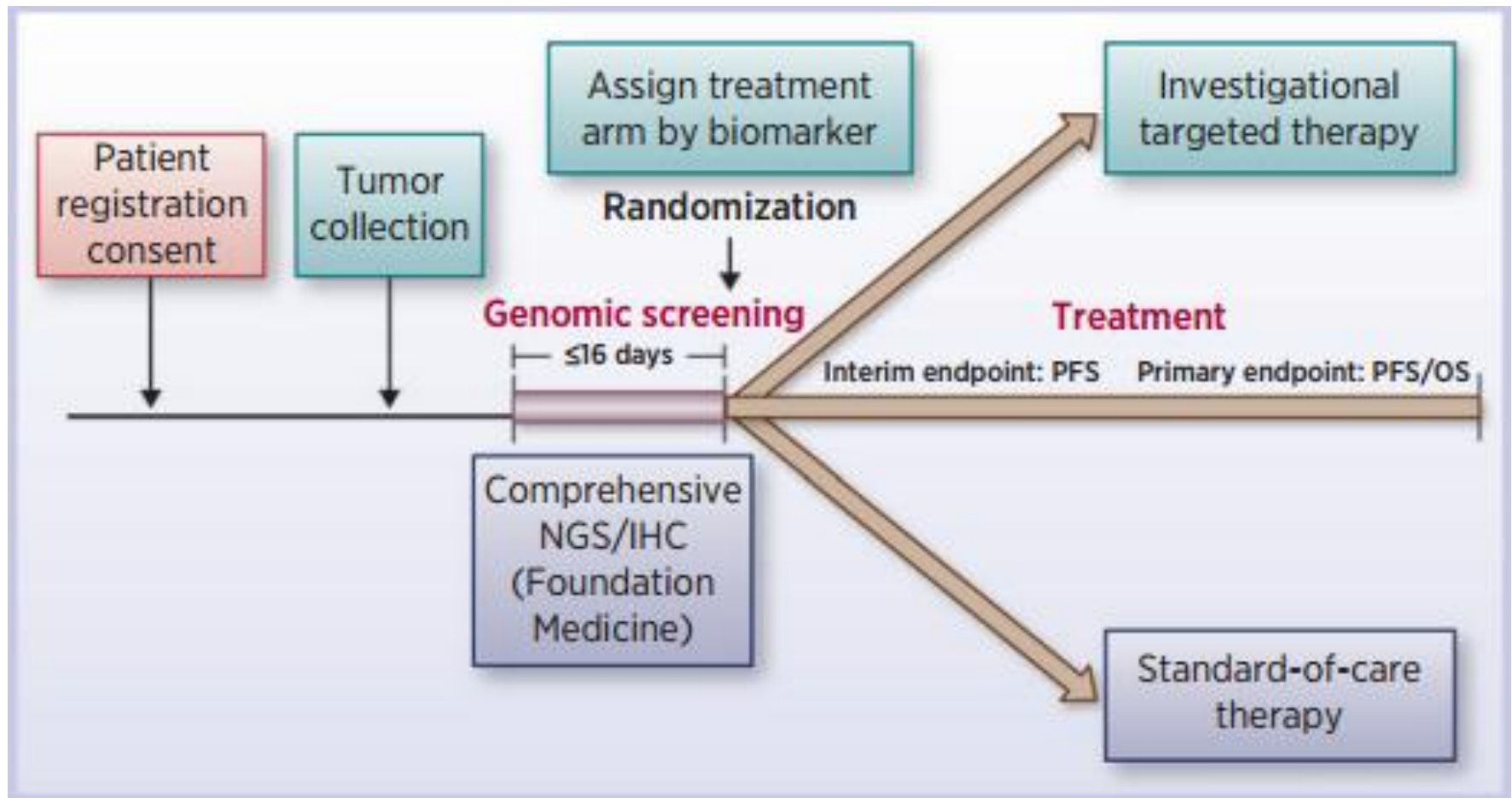
# MD Anderson Lung Cancer Program

## Personalized Therapy Strategy in NSCLC

### Tissue and Blood Collection

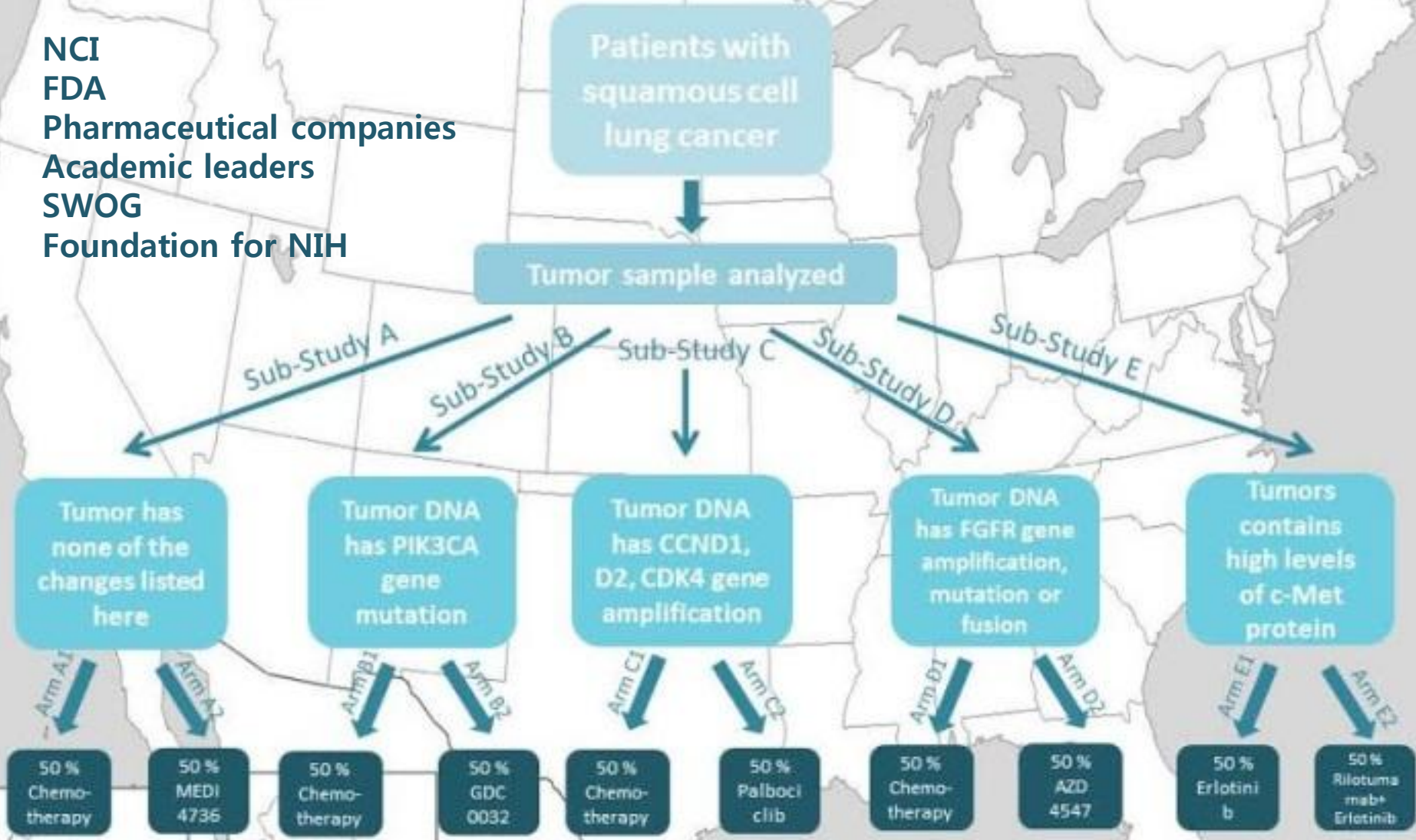


**Lung Master Protocol (Lung-MAP)—A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400**



# Lung-MAP Trial Arms for Treatment

NCI  
FDA  
Pharmaceutical companies  
Academic leaders  
SWOG  
Foundation for NIH



# National Lung Matrix Trial

18 UK Experimental Cancer Medicine Centres



AstraZeneca/MedImmune  
Pfizer

PRE-SCREENING

NGS SEQUENCING

MATRIX LUNG STUDY

## Molecular cohorts and initial estimated prevalence rates

		AZD4547	AZD2014	Palbociclib	Crizotinib	Selumetinib + docetaxel	AZD5363	AZD9291
		Arm A	Arm B	Arm C	Arm D	Arm E	Arm F	Arm G
A1: FGFR2/3 mutation—NSCLC [4, 5]	ADC <1.0% SCC 4.0%	✓						
B1: TSC1/2 mutation—NSCLC [4]	ADC <1.0% SCC 2.7%		✓					
B2: LKB1 mutation—NSCLC [4, 5]	ADC 8.8% SCC 1.6%		✓					
C1: Proficient Rb and p16 loss—SCC [4]	SCC 29.0%			✓				
C2: Proficient Rb and p16 loss—ADC [4]	ADC 19.6%			✓				
C3: Proficient Rb and CDK4 amplification—NSCLC [4, 5]	ADC 7.0% SCC <1.0%			✓				
C4: Proficient Rb and CCND1 amplification—NSCLC [4, 5]	ADC 5.0% SCC 12.0%			✓				
C5: Proficient Rb and KRAS mutation—ADC [5]	ADC 25.8%			✓				
D1: Met amplified—NSCLC	ADC 2.7% SCC 1.4%				✓			
D2: ROS1 rearranged—NSCLC [6]	ADC 1.7% SCC <1.0%				✓			
E1: NF1 mutation—SCC [4]	SCC 5.8%					✓		
E2: NF1 mutation—ADC [4]	ADC 4.6%					✓		
E3: NRAS mutation—ADC [7]	ADC 0.7%					✓		
F1: PIK3CA mutation—SCC [8]	SCC 11.0%						✓	
F2: PIK3CA amplification—SCC [4]	SCC 15.0%						✓	
F3: PI3K/AKT deregulation								
PI3KCA mutation and amplification—ADC [8]	ADC 2.0%						✓	
PTEN mutation and loss (ADC) [5]	ADC 3.0%							
AKT1 mutation (NSCLC) [4, 5]	ADC 0.5% SCC 0.5%							
F4: PTEN loss and mutation—SCC [4]	SCC 20.0%						✓	
G1: EGFR mutation and T790M + NSCLC	ADC 8% SCC <1%							✓



# Umbrella trials in **Adjuvant** chemotherapy

## **ALCHEMIST trial**

(Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)

---

# Prior studies of **adjuvant targeted therapies** in NSCLC

Trial	Disease	Treatment	Exposure	Primary endpoint	DFS	OS
NCIC CTG BR.19 trial (21)	NSCLC, no molecular selection	Gefitinib vs. placebo (1:1)	2 years	OS	HR 1.22 (0.99-1.51); median 6.3 years	HR 1.24 (0.94-1.64); P=0.14; median 5.1 years; at 6.3 years, 54%
RADIANT trial (22)	NSCLC, EGFR+ by IHC or FISH	Erlotinib vs. placebo (2:1)	2 years	DFS	HR 0.90 (0.74-1.11); median 50.5 months; 48.2 months	HR 1.03 (0.88-1.45); P=0.3350
D'Angelis et al. (23)	NSCLC, EGFR mutant (retrospective analysis)	Erlotinib or gefitinib [84] vs. no adjuvant TKI [202]	Median 18.6 months (0.1-51.4)	Retrospective	HR 0.43 (0.26-0.72) P=0.001	HR 0.50 (0.23-1.08) P=0.076
SELECT trial (24)	NSCLC, EGFR mutant	Erlotinib	2 years	DFS	90% at 2 years	92% at 2 years

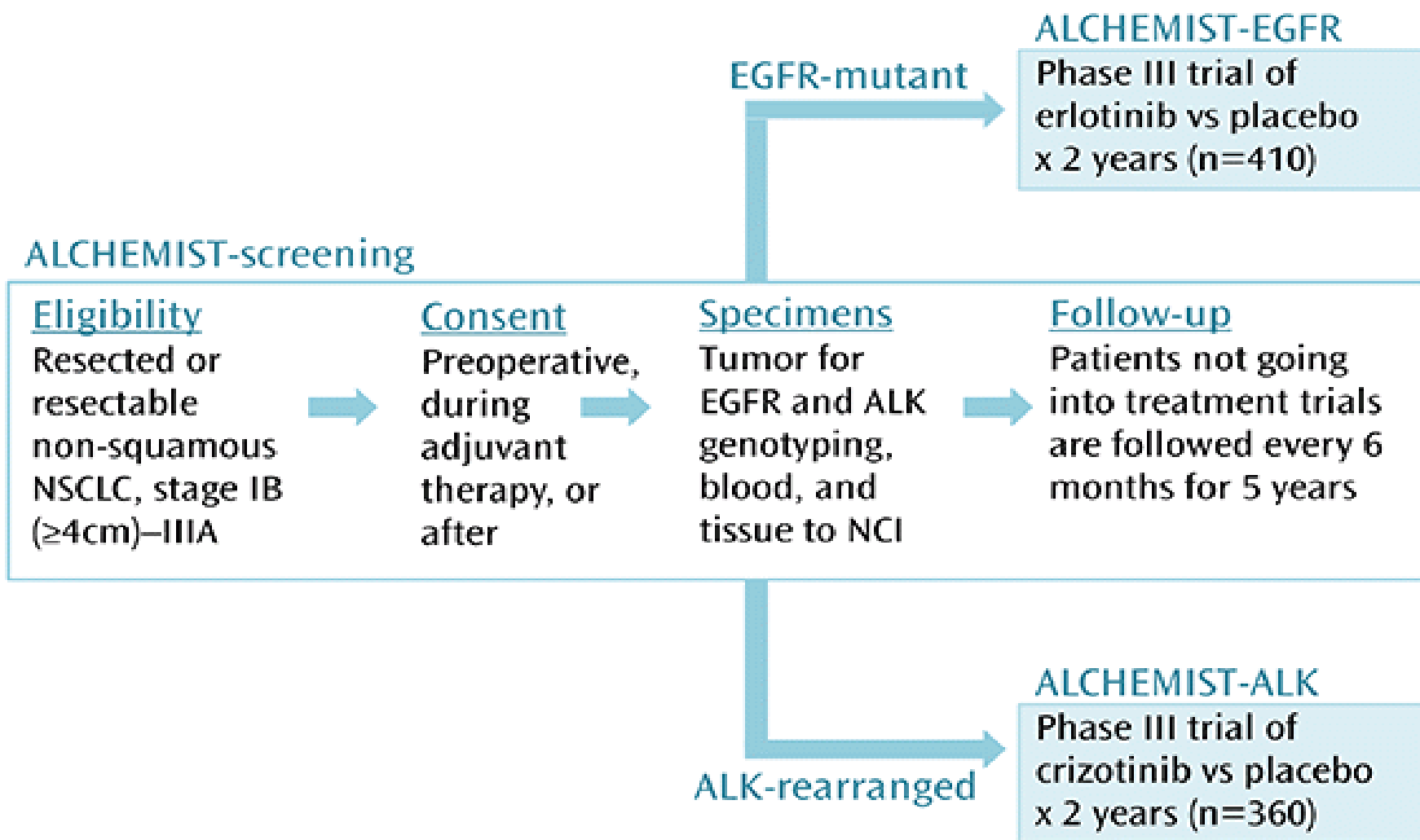
**Fail**

**Fail**

90% at 2 years      92% at 2 years

NSCLC, non-small cell lung cancer; DFS, disease free survival; OS, overall survival; HR, hazard ratio; NR, not reached; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

# ALCHEMIST Structure



# ALCHEMIST : Statistical Design Elements

<b>Trial Category</b>	<b>ALCHEMIST Screening Trial A151216</b>	<b>ALCHEMIST ALK Treatment Trial E4512 (± crizotinib)</b>	<b>ALCHEMIST EGFR Treatment Trial A081105 (± erlotinib)</b>
<b>Target</b>	<b>Registry/Intervention with biopsy at recurrence</b>	<b>ALK rearrangement</b>	<b>EGFR mutation</b>
<b>Prevalence of Target</b>		<b>~5%</b>	<b>~10%</b>
<b>Total Sample Size</b>	<b>6000 – 8000</b>	<b>378 (5% ineligible)</b>	<b>430 (5% ineligible)</b>
<b>Primary Endpoint</b>	<b>Correlative endpoints &amp; epidemiology</b>	<b>Overall survival</b>	<b>Overall survival</b>
<b>Power</b>		<b>80%</b>	<b>85%</b>
<b>One-sided <math>\alpha</math></b>		<b>0.05</b>	<b>0.05</b>
<b>Hazard Ratio</b>		<b>0.67</b>	<b>0.67</b>

# ALCHEMIST Support

- Agents are being **supplied** for the tx. trials by **Astellas (erlotinib)** and **Pfizer (crizotinib)**
- **Testing for ALK and EGFR** is funded by **NCI** and will be performed in a **central lab.** by **Response Genetics, Inc.**
- Research effort with **advanced genomic analysis** by the **NCI Center for Cancer Genomics**

# 한국인 폐암환자의 종양 유전체 유전자 지형 기반의 한국인 비소세포폐암 표적치료 최적화를 위한 공익적 다기관 임상연구

- 차세대염기서열분석 (NGS : Next Generation Sequencing)
  - 유전체 데이터베이스를 기반
  - 환자에게 맞춤형 표적치료를 제공
- **ALK** 억제제 세리티닙 (ceritinib, Zykadia™)
- **BRAF** 억제제 다브라페닙 (dabrafenib, Tafinlar)
- **MEK** 억제제 트라메티닙 (trametinib, Mekinist)
- **EGFR** 억제제 EGF816
- **C-Met** 억제제 INC280
- 면역항암제 PDR001 (**anti-PD-1** Monoclonal Ab, Novartis)

# 새로운 임상연구 디자인의 장점

## PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

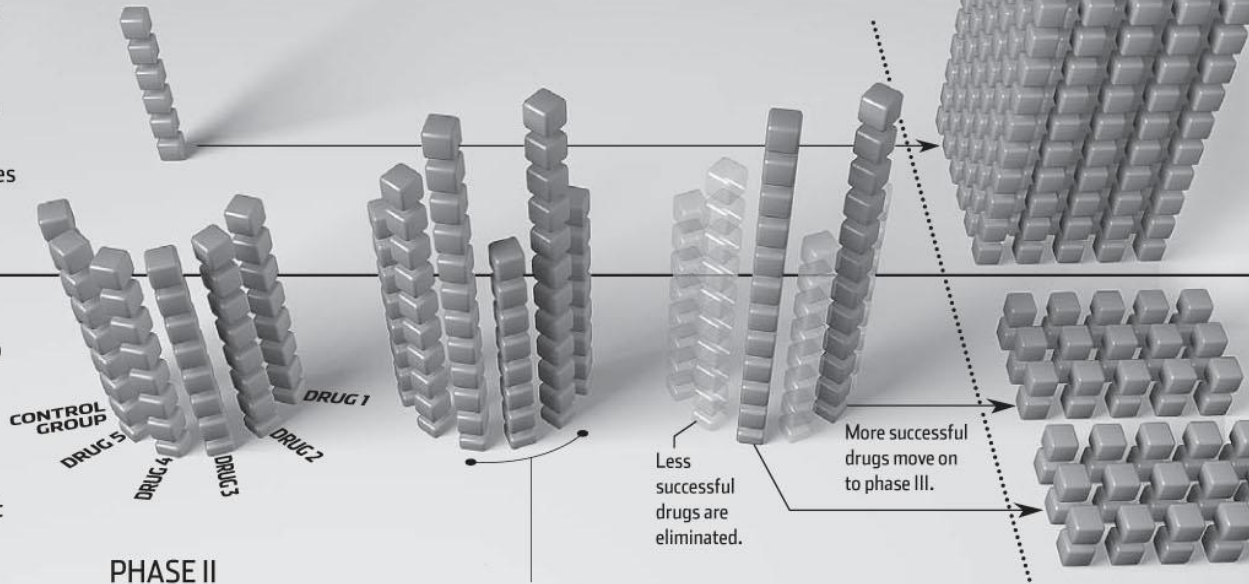
1 cube = 10 patients

### Traditional clinical trial

Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

### PHASE II

**Randomized or non-randomized trial:** In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.



### New trial design

Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

### PHASE II

Patients are placed in groups based on genetic profiles and are randomly assigned to either **standard therapy or one of five different drugs** plus standard care.

Early results increase chances that **patients entering the trial later will be assigned to a drug showing benefit** against tumors with their genetic profile.

It will take up to 120 patients for each drug to determine **which ones graduate to phase III studies.**

### PHASE III

If a drug graduates to phase III, it typically takes **3,000 patients** and about three years to determine if it is safe and effective enough for approval.



**HISTORIC SUCCESS RATE**  
**30 TO 40%**

### PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with **300 patients** selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.



**PROBABILITY OF SUCCESS**  
**85%**

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Marianne Murray/WSJ

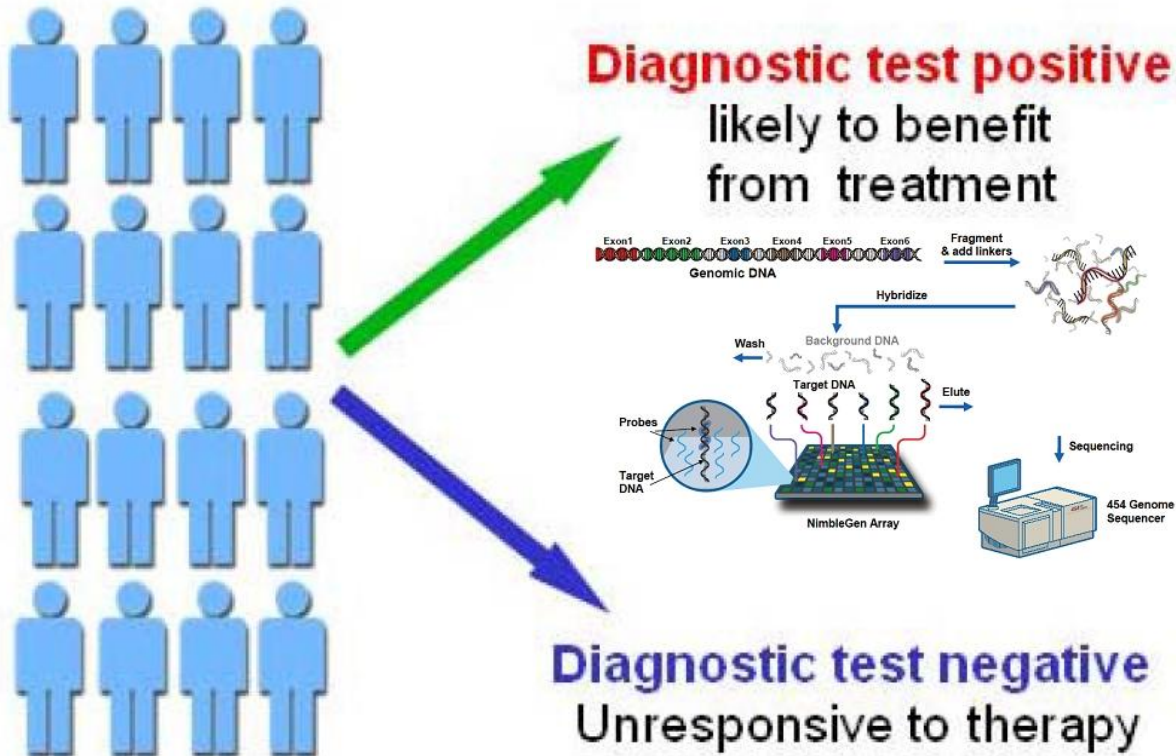
Source: Donald Berry, M.D. Anderson Cancer Center

**Reduce time, resource, and patient numbers**

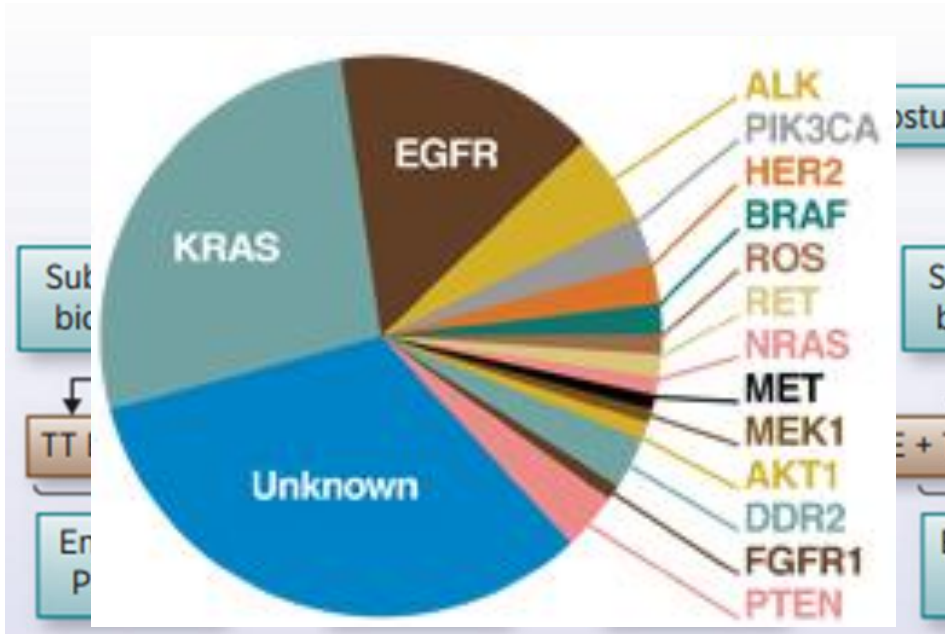


## Umbrella Trial 성공의 필요조건

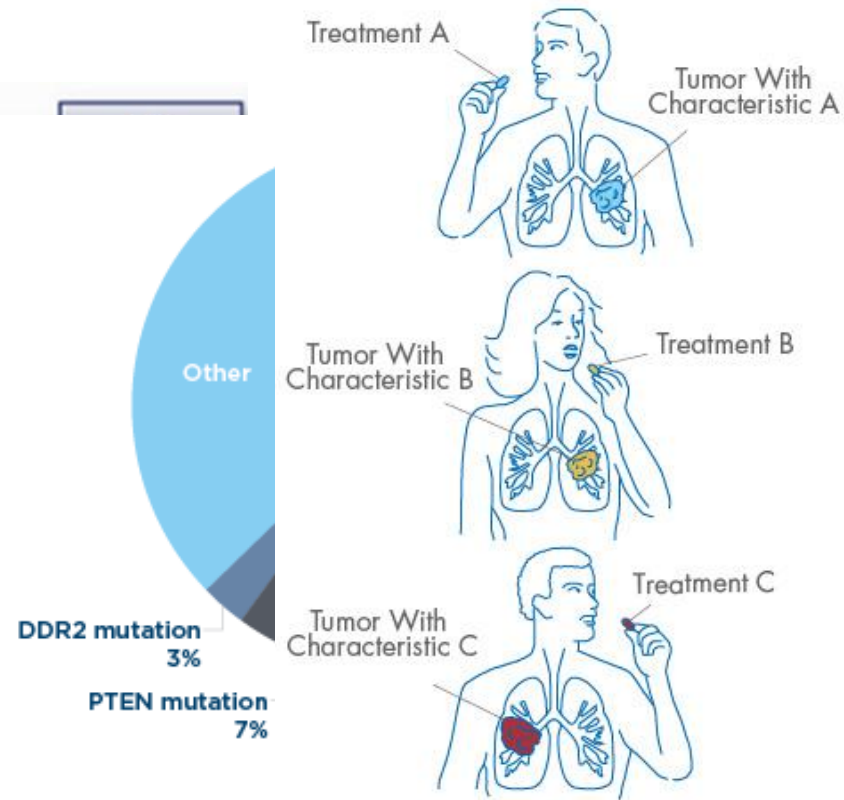
# 맞춤의료의 시대와 새로운 디자인의 임상시험



# 맞춤의료의 시대와 새로운 디자인의 임상시험



Adenocarcinoma



Squamous cell carcinoma



# 결론



## Umbrella trial

- 다양한 분자생물학적 표적을 갖고 있는 폐암 환자에게 가장 적합한 치료 약제의 선택을 제시할 수 있는 새로운 임상방법
- 다양한 표적을 찾을 수 있는 진단방법의 발전과 그러한 표적을 치료하는 약제 개발의 상호협력이 필요
- 성공 요인 : 임상시험 전문의, BT 기술자, 생물통계학자, 제약회사, 정부기관 등이 같이 참여하는 시스템 개발이 필요

Q&A

Thank you for your attention  
경청해 주셔서 감사합니다

Molecular cohorts and initial estimated prevalence rates

AZD4547 AZD2014 Palbociclib

Arm A Arm B Arm C

A1: FGFR2/3 mutation—NSCLC [4, 5]

ADC <1.0%

✓

SCC 4.0%

B1: TSC1/2 mutation—NSCLC [4]

ADC <1.0%

✓

SCC 2.7%

B2: LKB1 mutation—NSCLC [4, 5]

ADC 8.8%

✓

SCC 1.6%

C1: Proficient Rb and p16 loss—SCC [4]

SCC 29.0%

✓

C2: Proficient Rb and p16 loss—ADC [4]

ADC 19.6%

✓

C3: Proficient Rb and CDK4 amplification—NSCLC [4, 5]

ADC 7.0%

✓

SCC

<1.0%

C4: Proficient Rb and CCND1 amplification—NSCLC [4, 5]

ADC 5.0%

✓

SCC

12.0%

C5: Proficient Rb and KRAS mutation—ADC [5]

ADC 25.8%

✓

Molecular cohorts and initial estimated prevalence rates

		Crizotinib Arm D	Selumetinib + docetaxel Arm E	AZD5363 Arm F	AZD9291 Arm G
D1: Met amplified—NSCLC	ADC 2.7% SCC 1.4%	✓			
D2: ROS1 rearranged—NSCLC [6]	ADC 1.7% SCC <1.0%	✓			
E1: NF1 mutation—SCC [4]	SCC 5.8%		✓		
E2: NF1 mutation—ADC [4]	ADC 4.6%		✓		
E3: NRAS mutation—ADC [7]	ADC 0.7%		✓		
F1: PIK3CA mutation—SCC [8]	SCC 11.0%			✓	
F2: PIK3CA amplification—SCC [4]	SCC 15.0%			✓	
F3: PI3K/AKT deregulation					
PI3KCA mutation and amplification—ADC [8]	ADC 2.0%			✓	
PTEN mutation and loss (ADC) [5]	ADC 3.0%				
AKT1 mutation (NSCLC) [4, 5]	ADC 0.5% SCC 0.5%				
F4: PTEN loss and mutation—SCC [4]	SCC 20.0%			✓	
G1: EGFR mutation and T790M + NSCLC	ADC 8% SCC <1%				✓