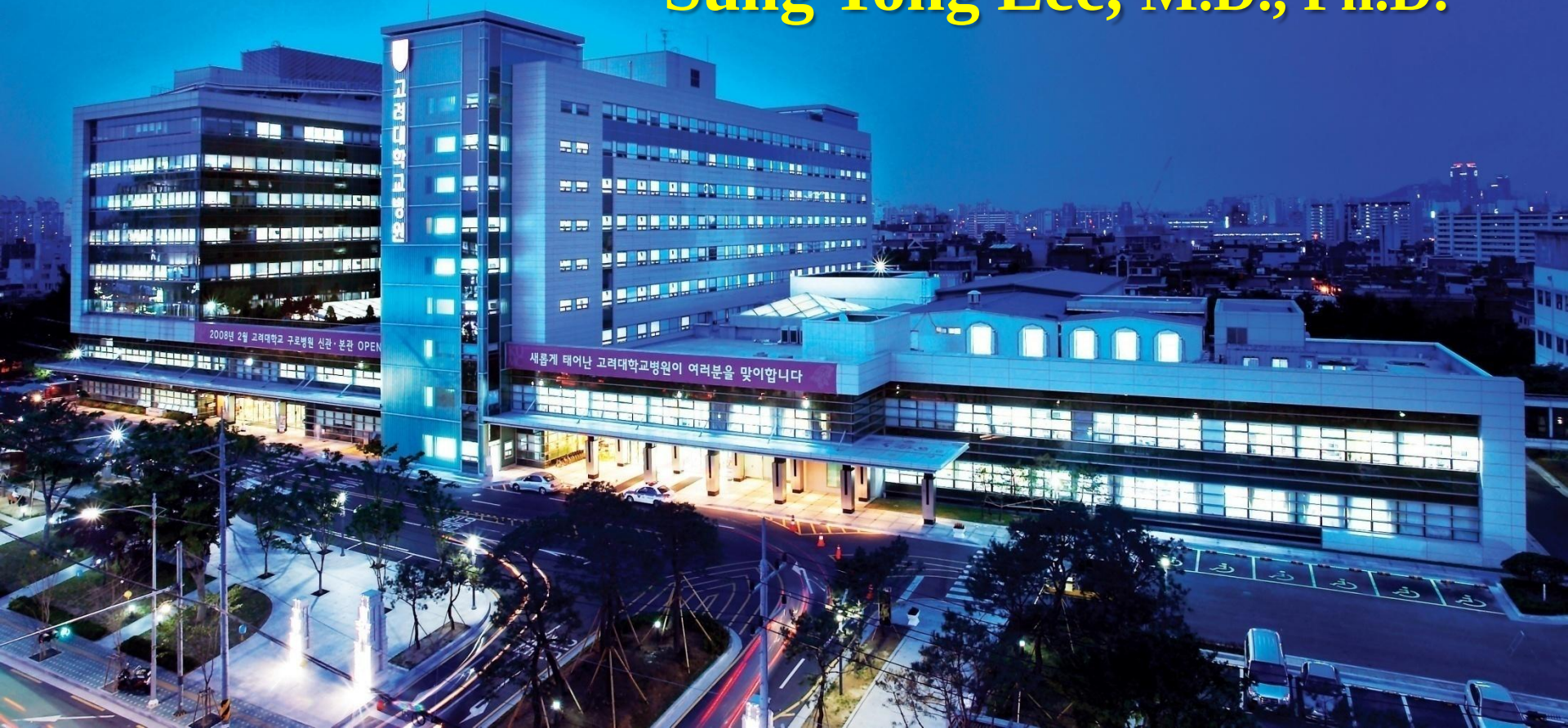
Umbrella trials for lung cancer treatment

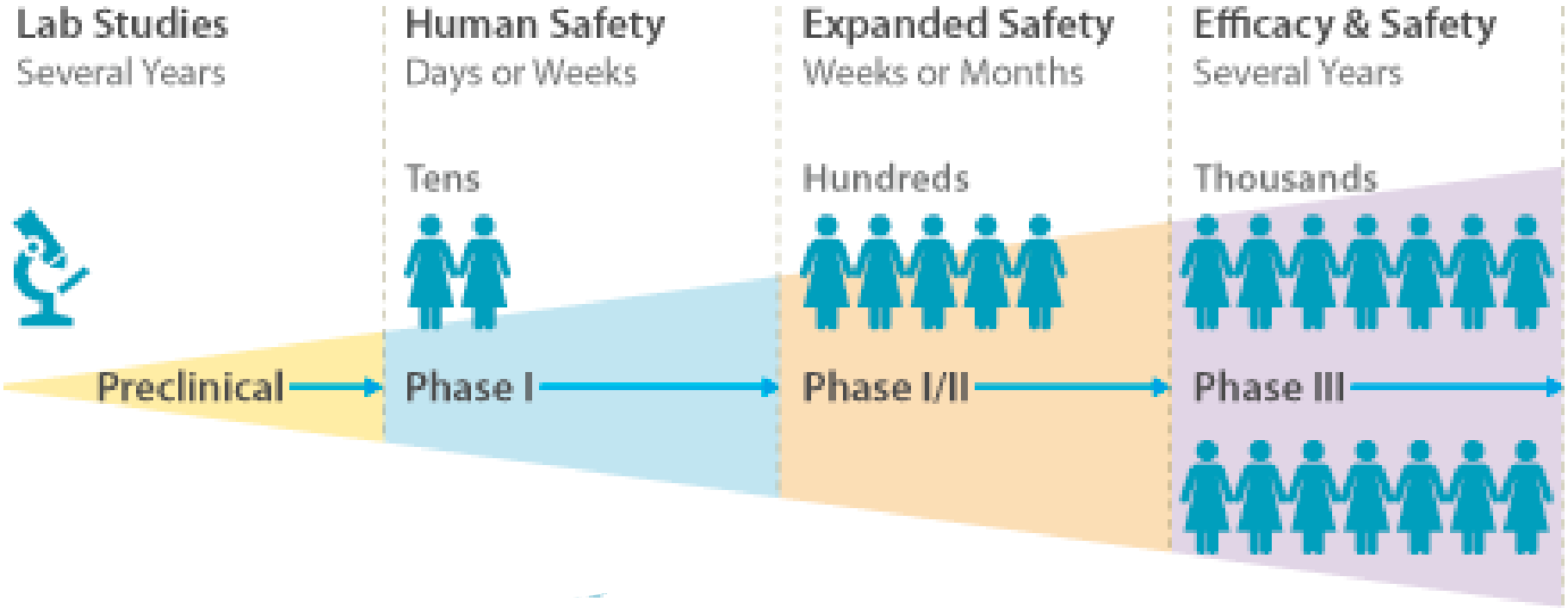
Korea University Medical Center

Department of Pulmonology and Critical Care Medicine

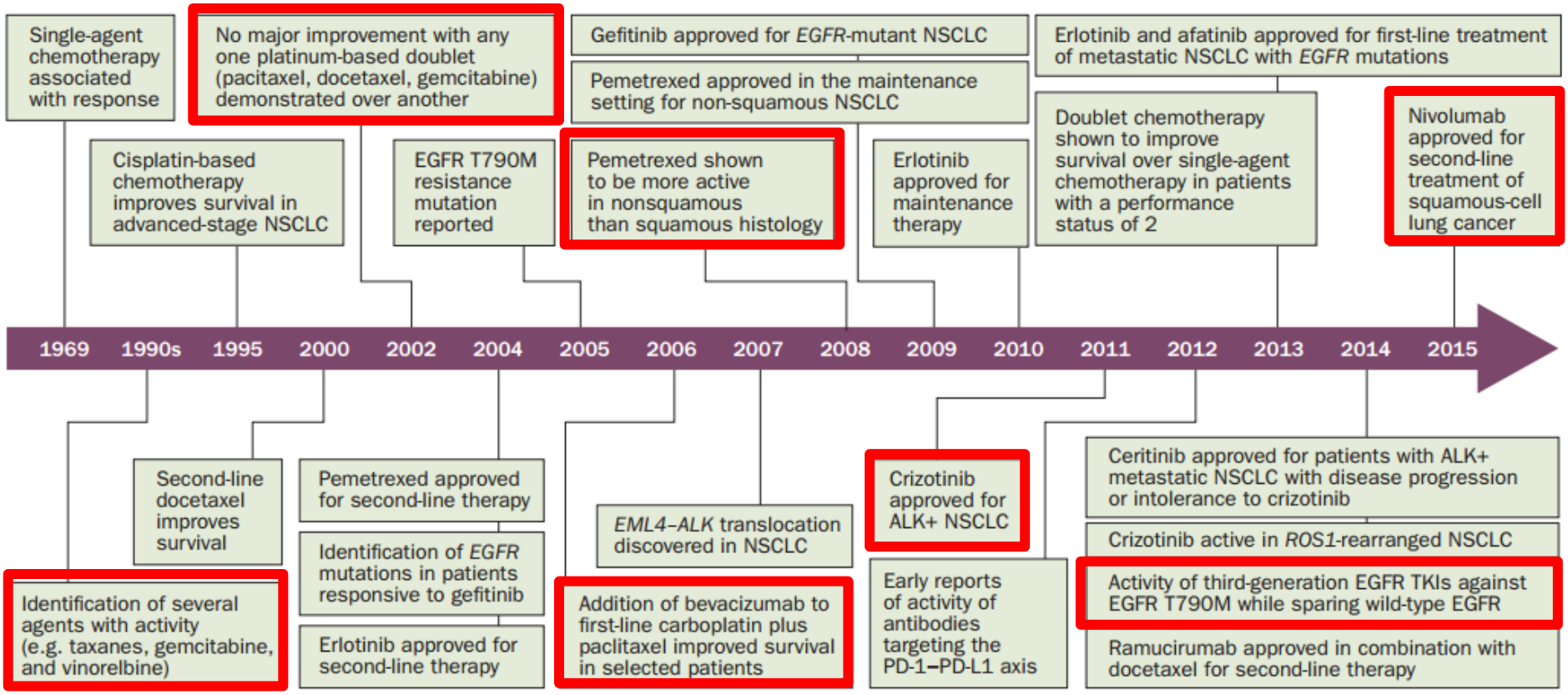
Sung Yong Lee, M.D., Ph.D.



Clinical Trial



Historical milestones in NSCLC treatment



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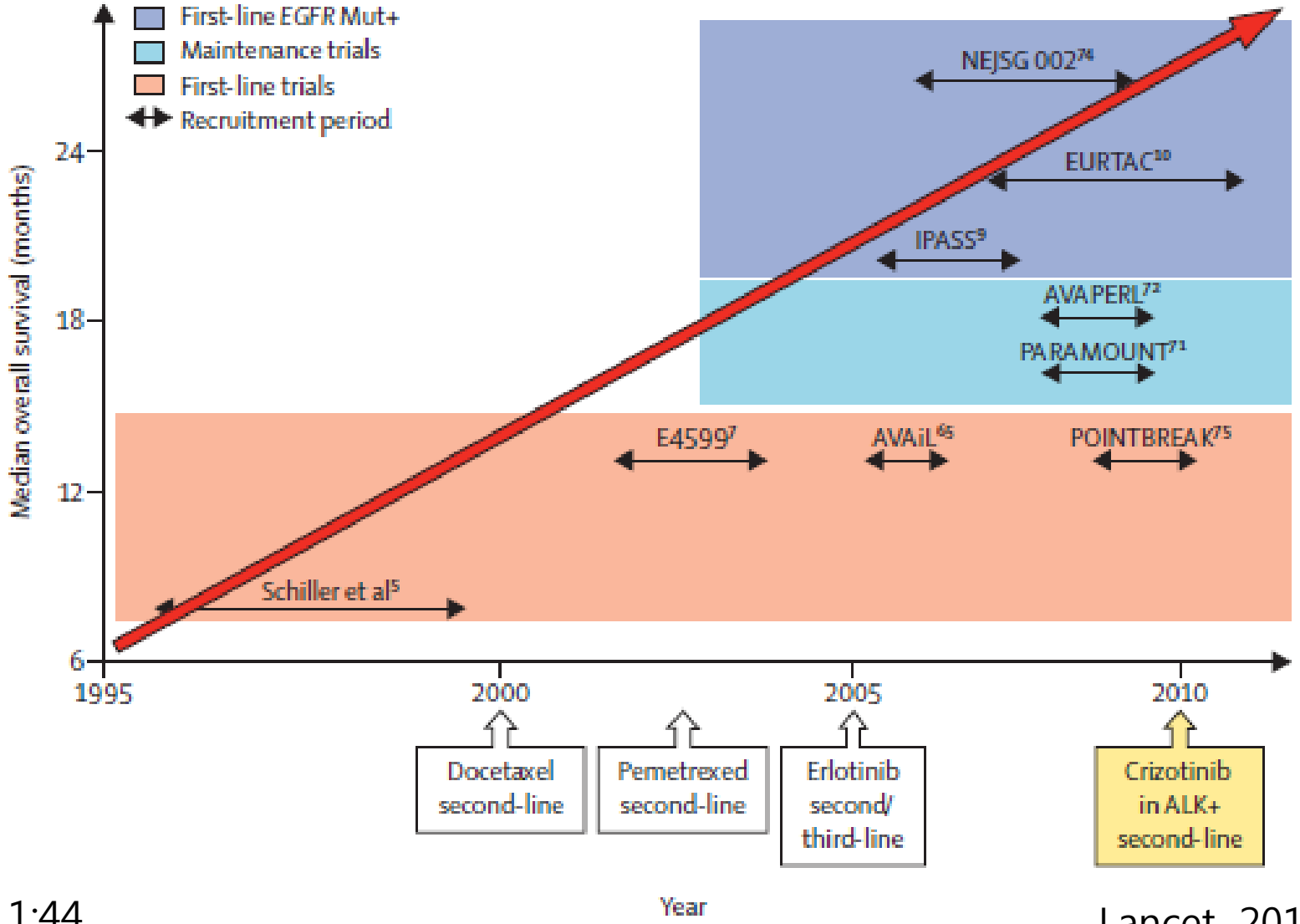
Success History of NSCLC Treatment



Lancet. 2013

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

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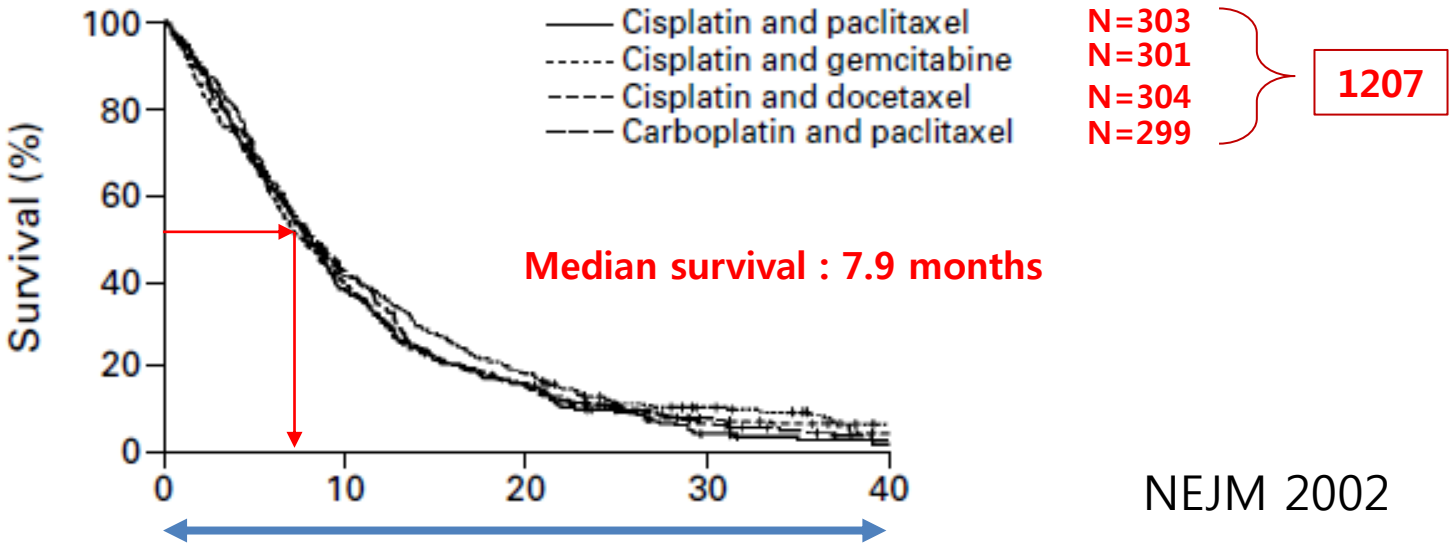

NEJM 2002

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Success story of Gefitinib

IDEALs
(Phase II)

gefitinib (n=1129)
placebo (n=563)

ISEL
(vs BSC)

ISEL, INTEREST

- Pre-treated setting
- Unselected population

INTEREST
(vs docetaxel)

First approval of
gefitinib
(Japan)

ISTANA
(vs docetaxel)

IPASS, WJTOG, NEJ002, First Signal, IFUM

- First-line setting
- *EGFR* mutation+ population

IPASS
(vs carboplatin / paclitaxel)

2002 2005 2007 2009 2011 2013

EGFR protein expression

EGFR gene copy number

EGFR mutations

WJTOG3405
(v

NEJ002
(vs ca

First Signal
(vs cisplatin / gemcitabine)

BSC : Best Supportive Care

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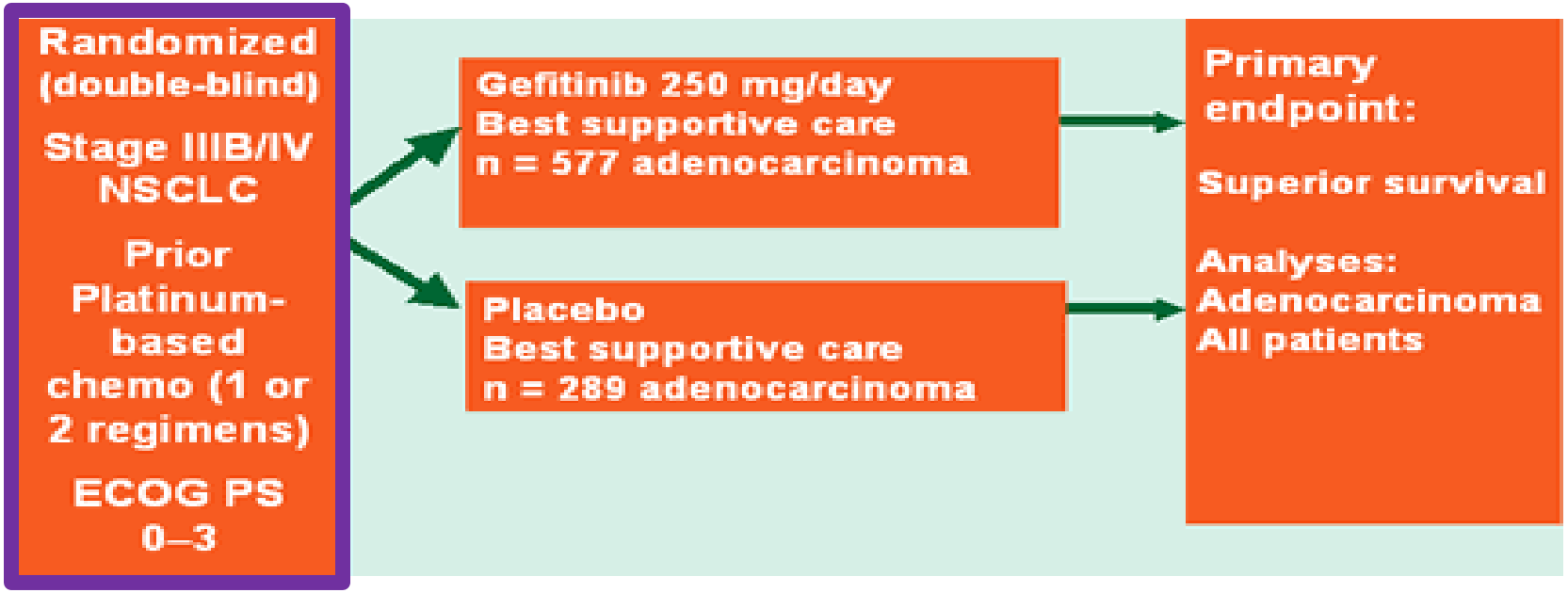
ISEL
(Gefitinib Survival Evaluation in Lung Cancer)



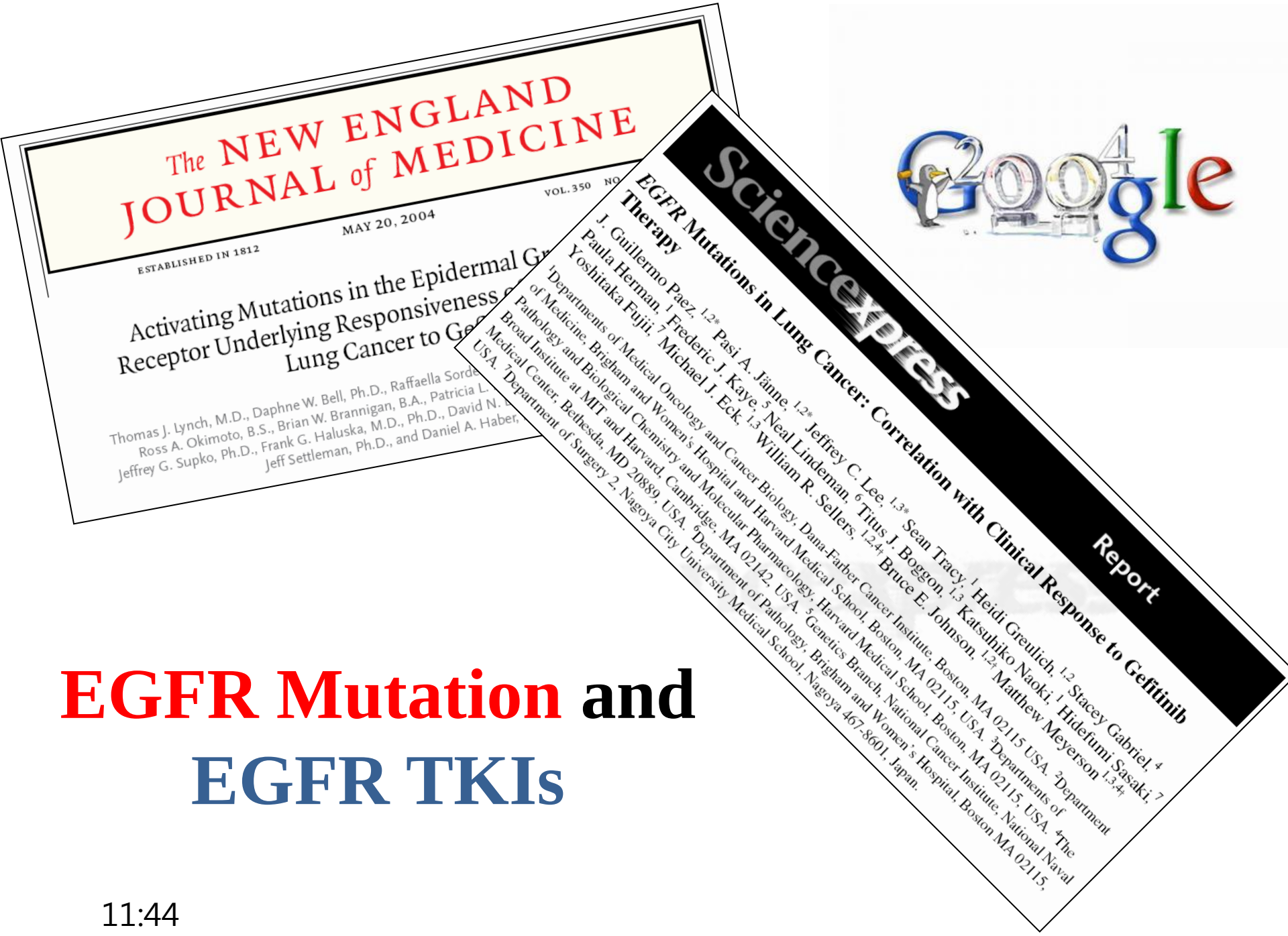
N=1692 patients

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



EGFR Mutation and EGFR TKIs

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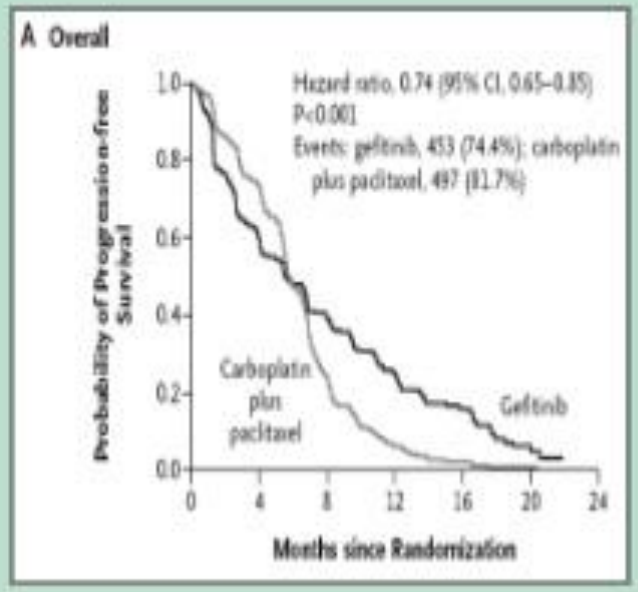
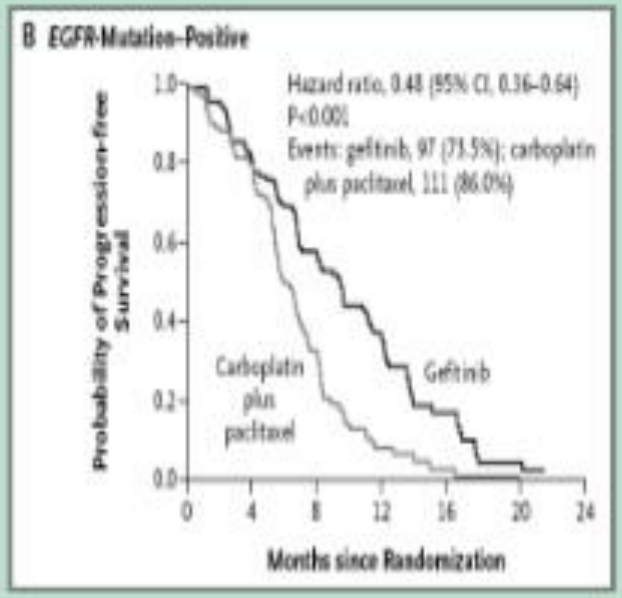
IPASS: Molecular Oncology Overrides Clinical Features

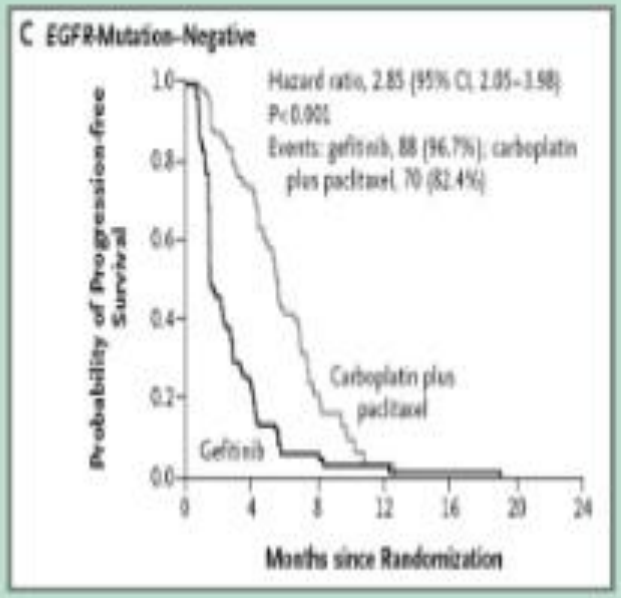
advanced lung adenocarcinoma,
Asian
no prior systemic Rx
Never or light ex-smoker

→ Carbo/paclitaxel x 6 cycles

→ Gefitinib daily until progression







Mok, NEJM 2009

A success story of gefitinib

IDEALs
(Phase II)

ISEL
(vs BSC)

ISEL, INTEREST

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WJTOG3405
(v

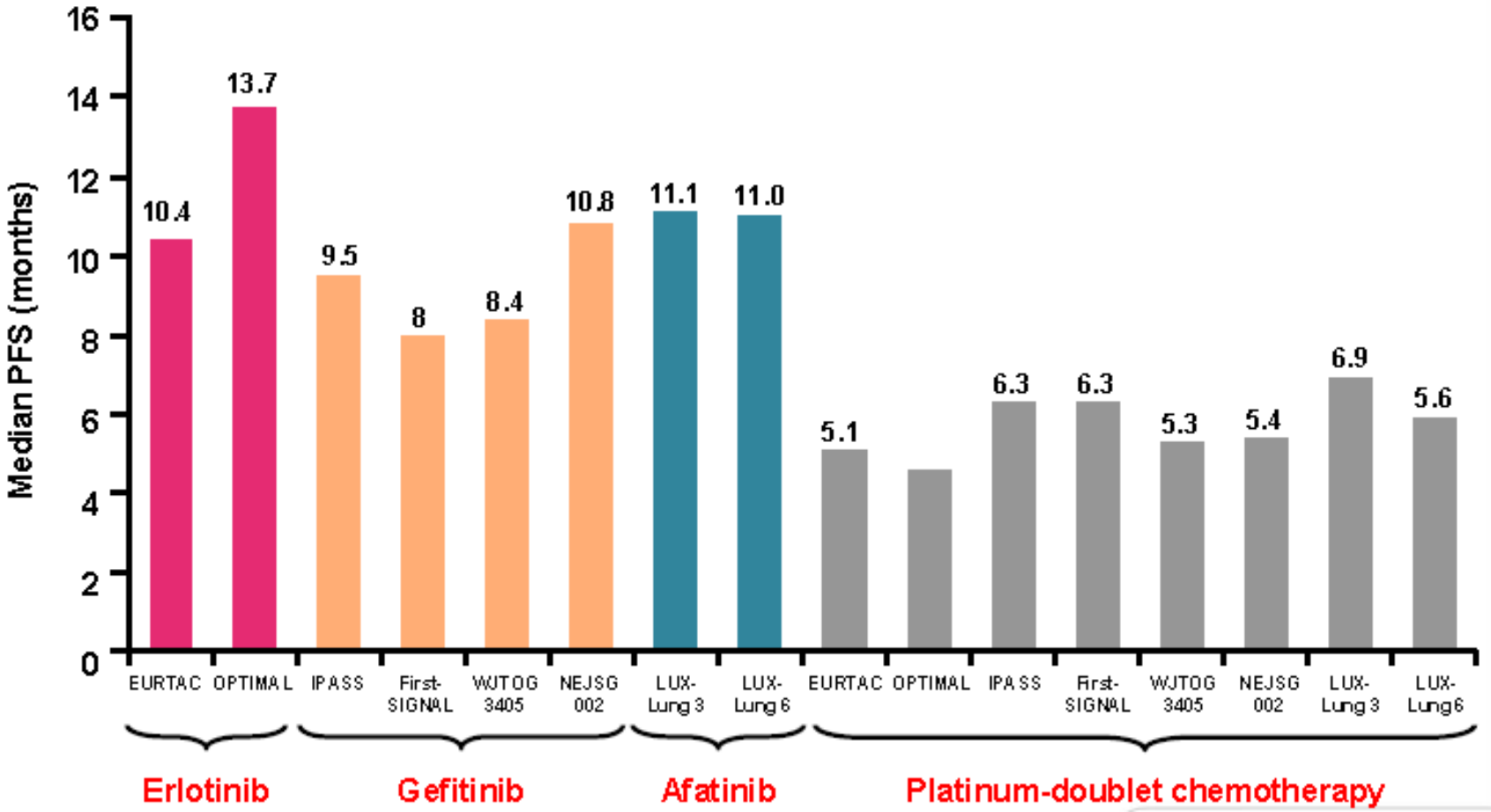
NEJ002
(vs ca

First Signal
(vs cisplatin / gemcitabine)

BSC : Best Supportive Care

11:44

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



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"JMDB" Randomized Phase III Trial of Cisplatin/Gemcitabine vs. Cisplatin/Alimta

First-line
Adv. NSCLC
(N = 1725)

Excluding pts with:
- **wt loss >10% body wt**
- **uncontrolled pleural effusions**

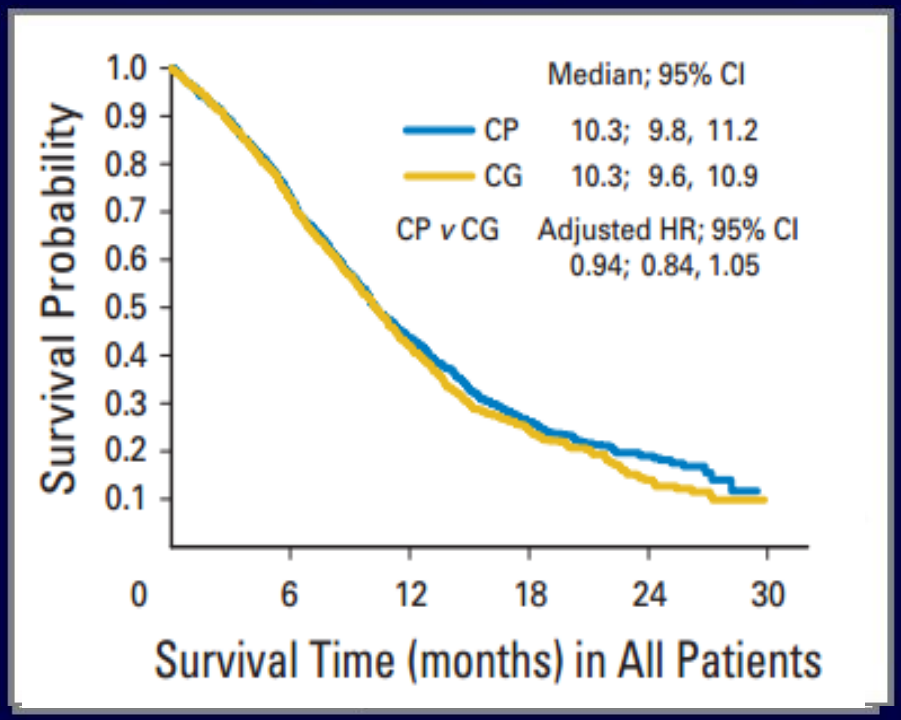
RANDOMIZED

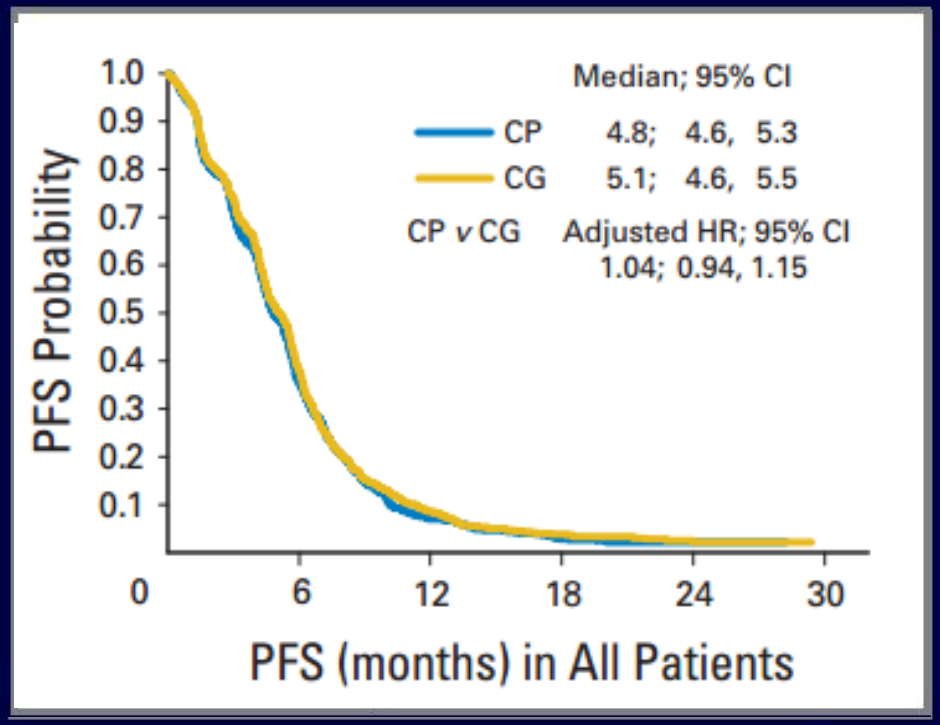
Cisplatin 75 mg/m2 IV day 1
Gemcitabine 1250 mg/m2 IV d1, 8
Every 21 days × 6 cycles
with B12 and folic acid supplementation

Cisplatin 75 mg/m2 IV day 1
Pemetrexed 500 mg/m2 IV d1
Every 21 days × 6 cycles
with B12 and folic acid supplementation

- **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

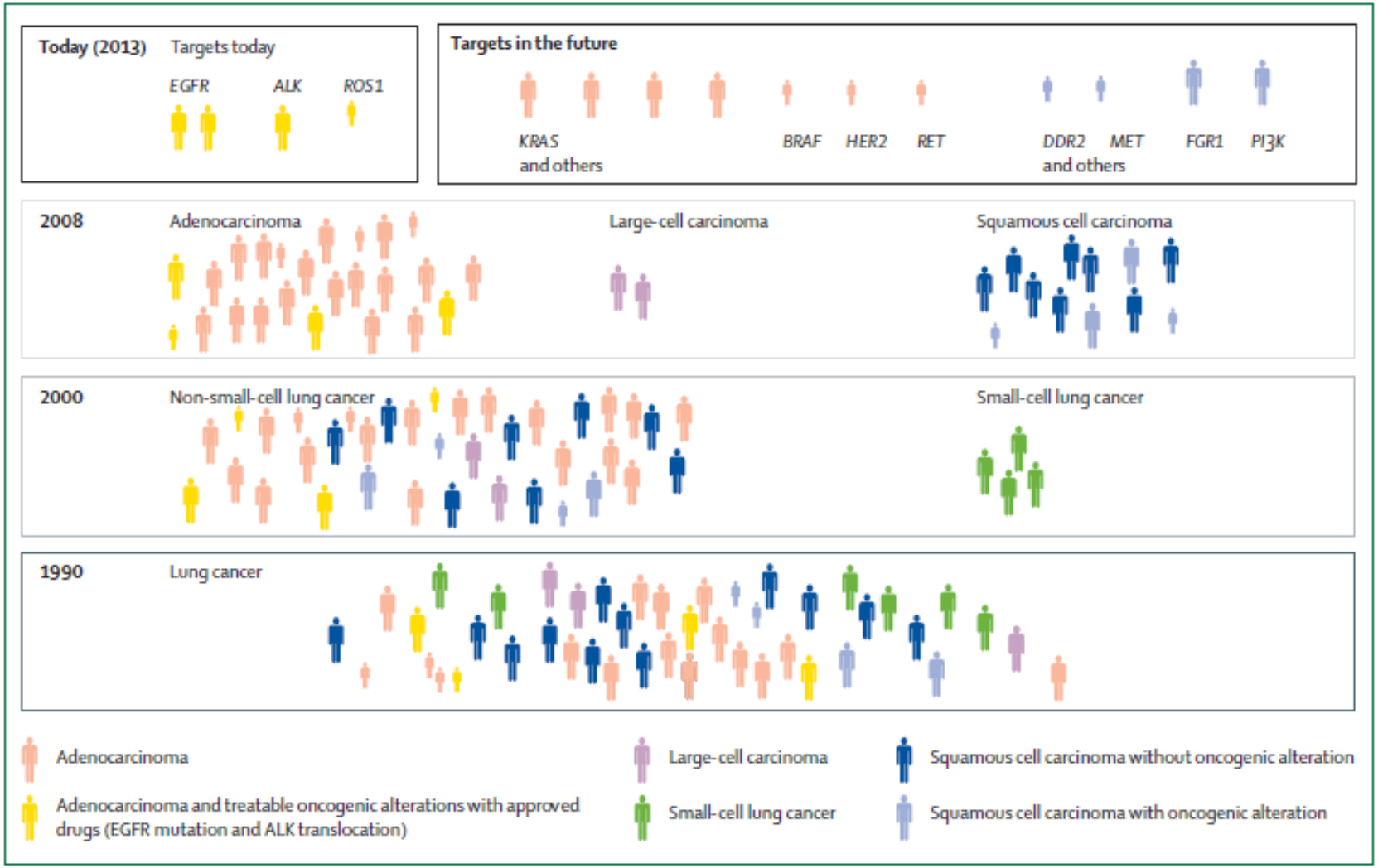
✓ 대상자들을 두 그룹으로 나눈다(control vs. case)

✓ 약효를 검증하고 그 메커니즘 검증을 위한 후속연구 필요

"trials designed to learn"

11:44

Heterogeneity of NSCLC: inter-individual



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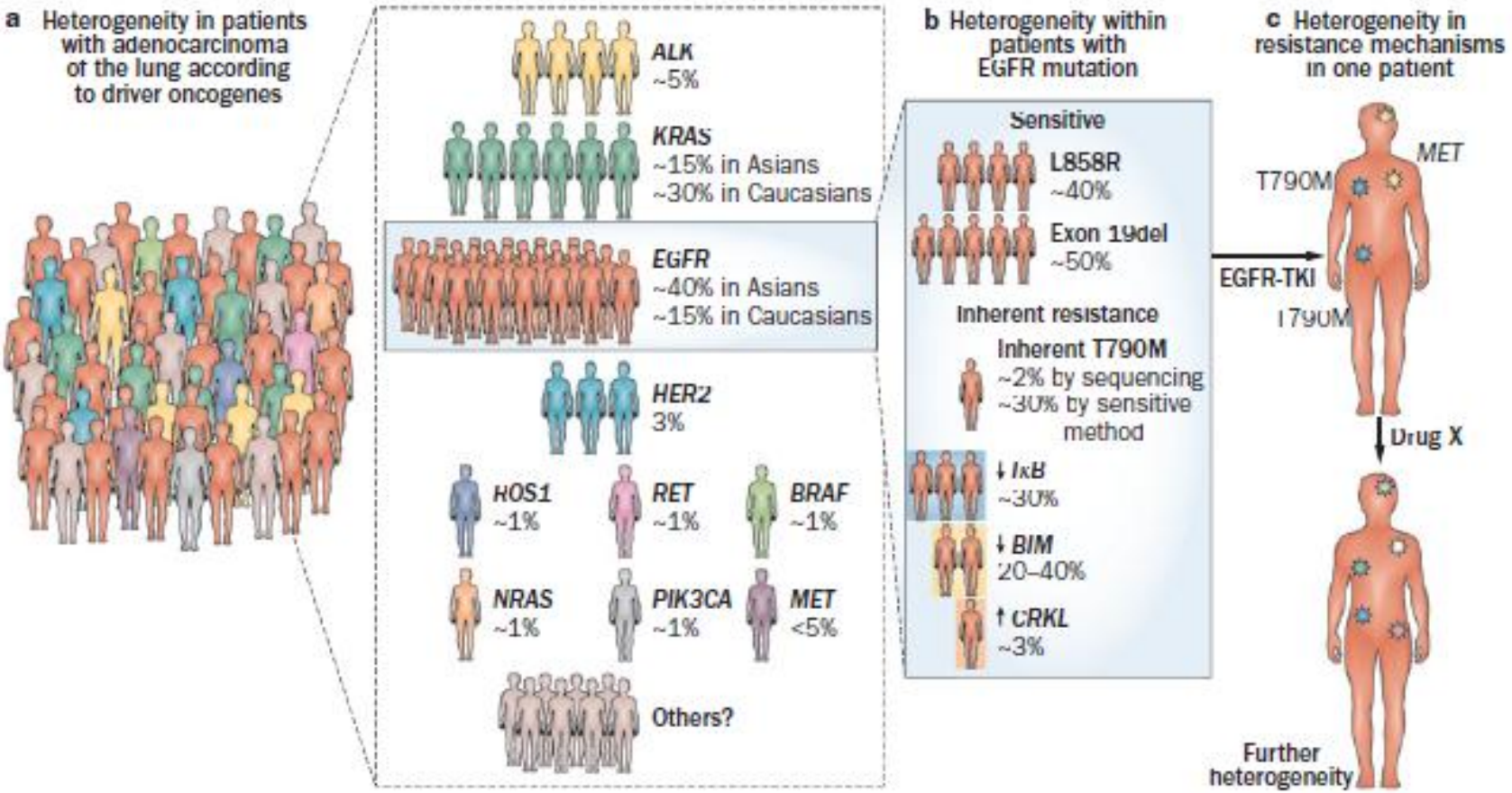
Lancet. 2013

Molecular Heterogeneity of NSCLC : intra-individual



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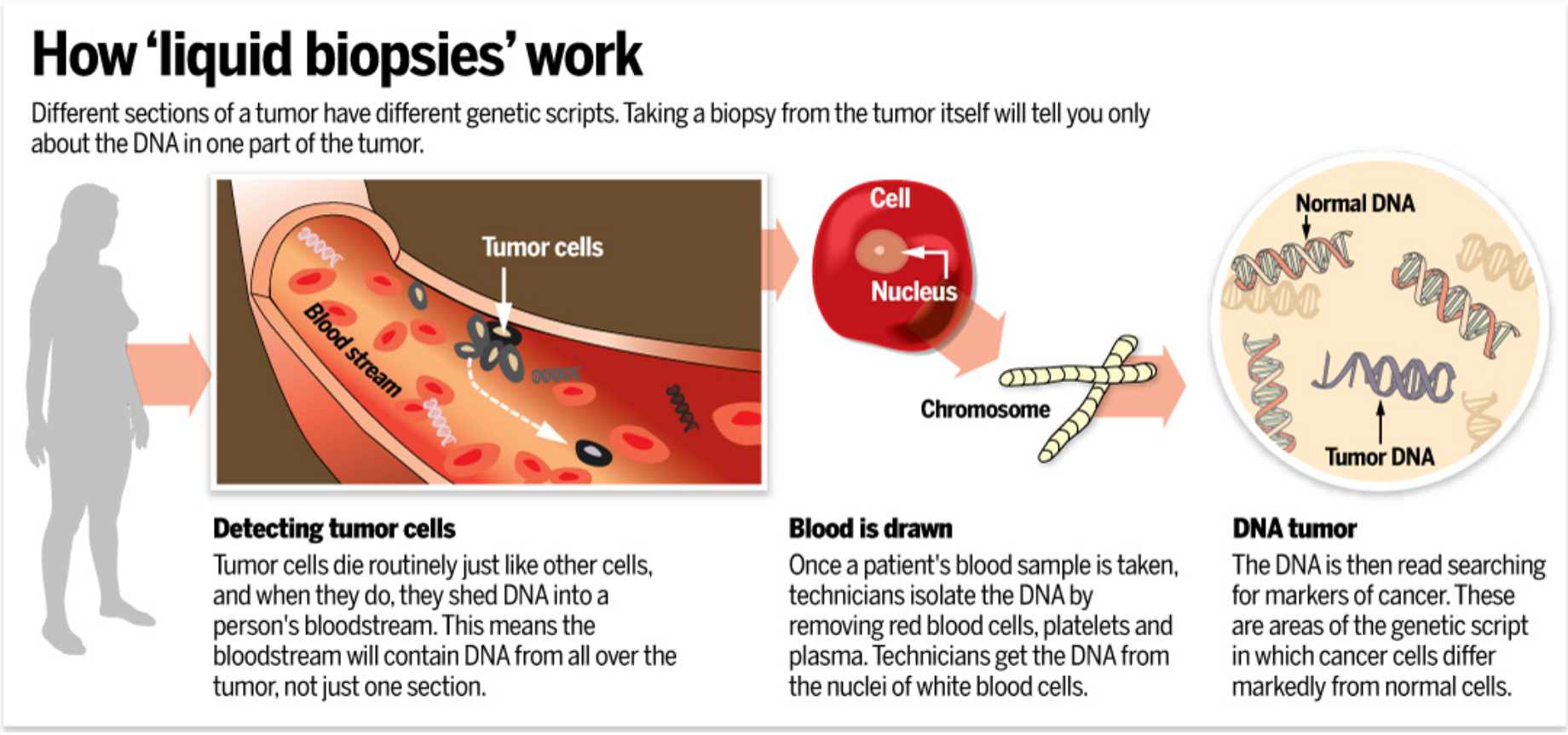
Nat Rev Clin Oncol. 2013

New Developments of Diagnostic Methods in Lung Cancer



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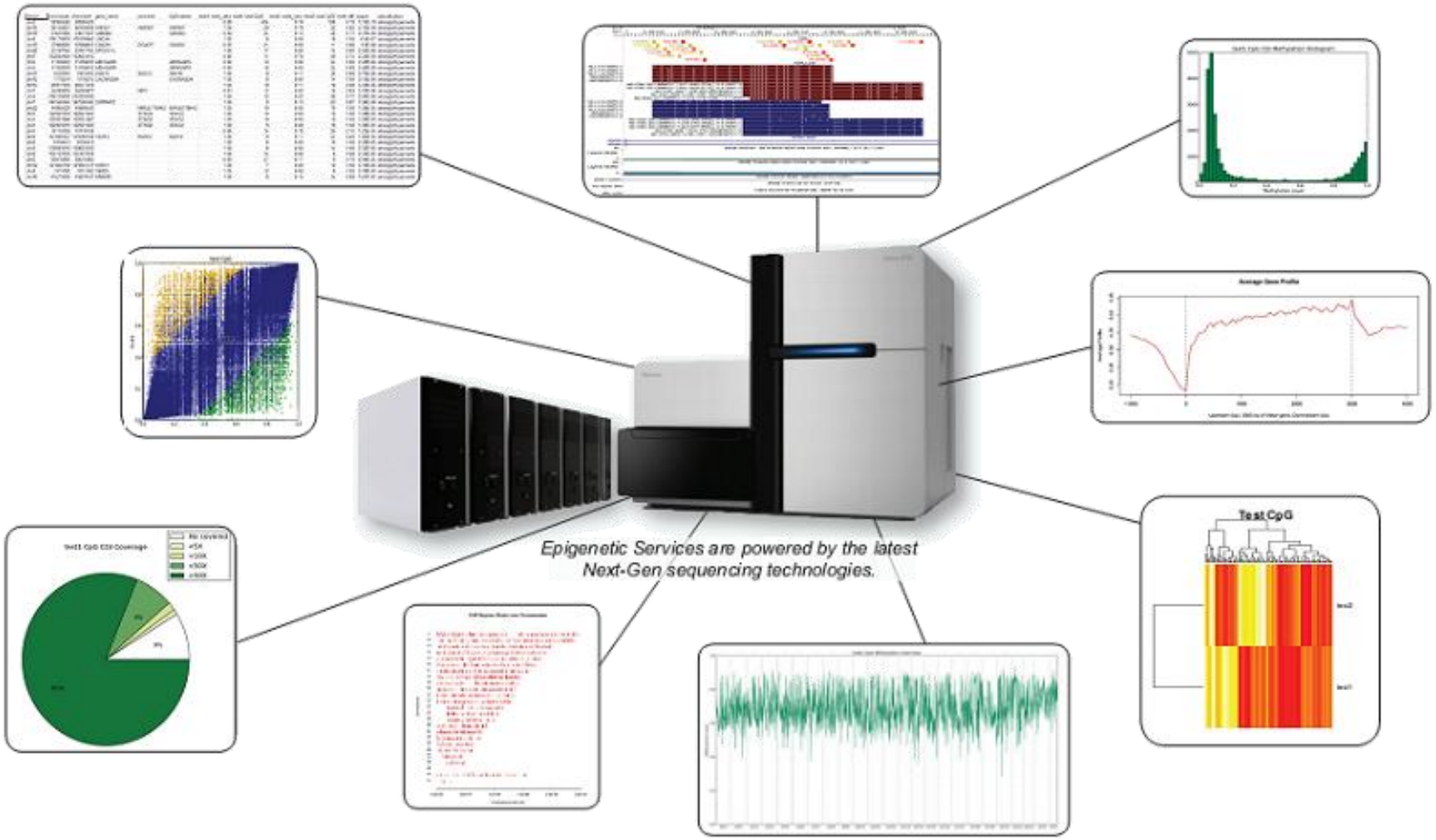
New Developments of Diagnostic Methods in Lung Cancer

Genotype-directed targeted therapies



분자생물학적 표적 vs. 표적치료제

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

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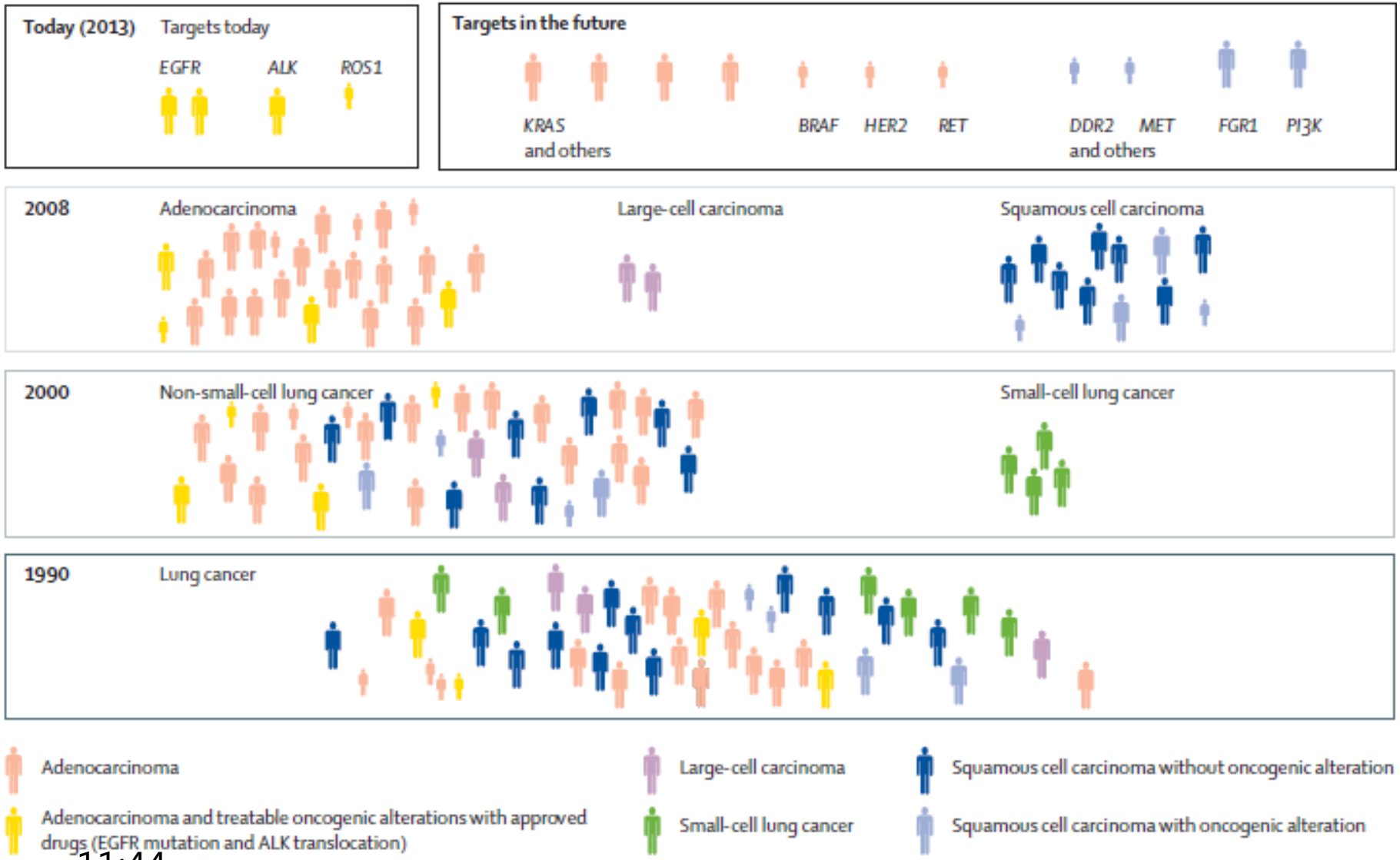
표적치료 ➡ 맞춤치료



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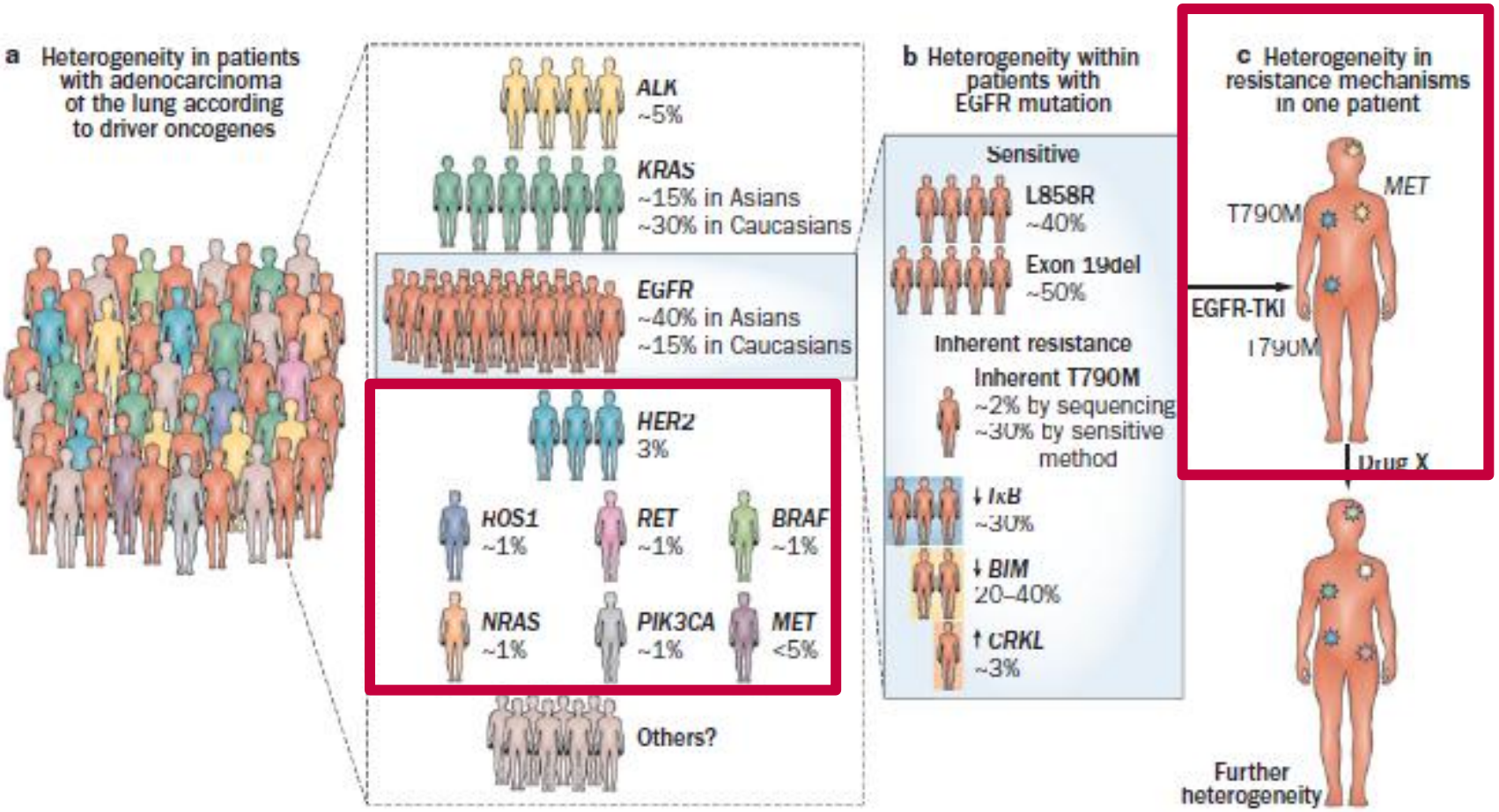
Lancet. 2013

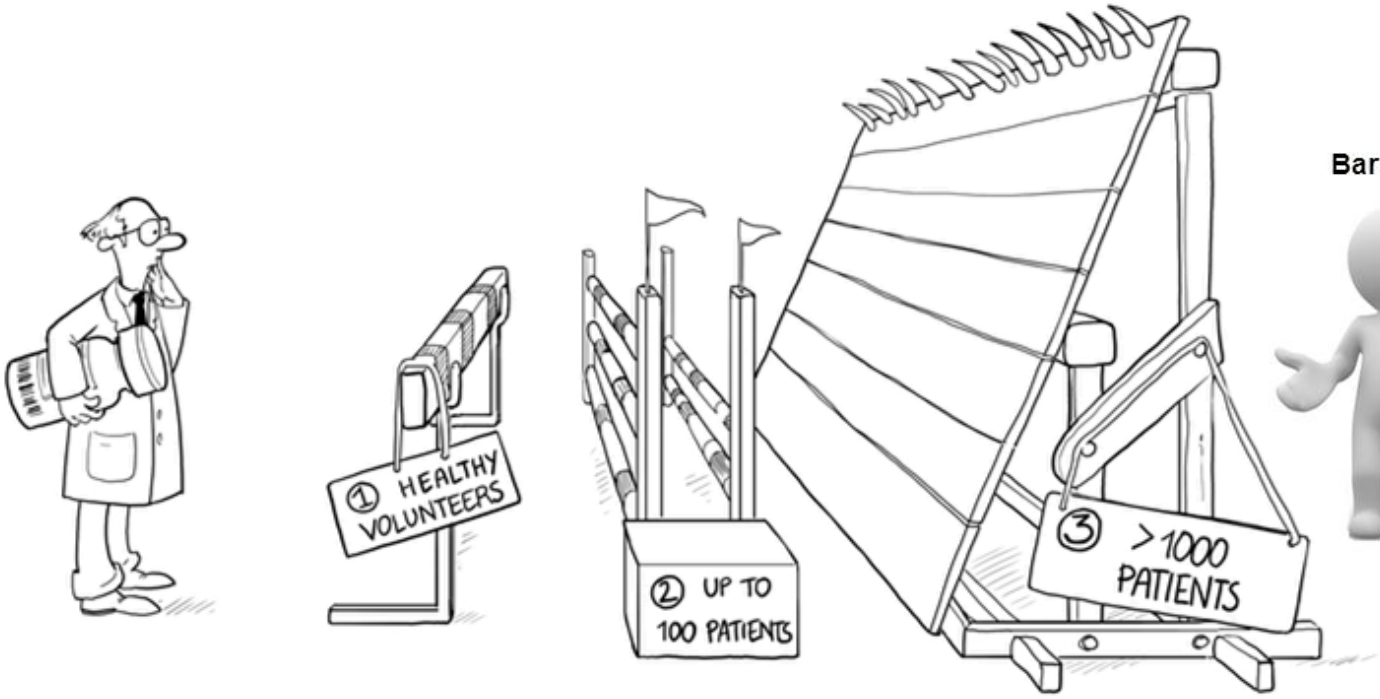
맞춤치료와 임상연구



Nat Rev Clin Oncol. 2013

Conventional Clinical Trials

~7.6 years for oncologic compounds



맞춤의료 (Personalized Medicine) 시대의 임상시험의 문제점

- ✓ **표적치료제**는 그 **유효성**이 **모든 환자에게서 동일**하게 나타나지 **않음**
- ✓ **과거** 특정 질병에 대해 **획일적인 치료방법**이 적용되었으나, **최근**에는 분자생물학적 진단의 개발로 개인의 **유전적 특성에 따른 맞춤치료**가 이루어짐.
- ✓ **소수의 환자들에서 발현**하는 **유전자**를 표적으로하는 임상시험의 경우 기존의 임상시험으로는 **시간, 돈, 인력의 문제점**들이 발생함 (screening failure rate가 높다).

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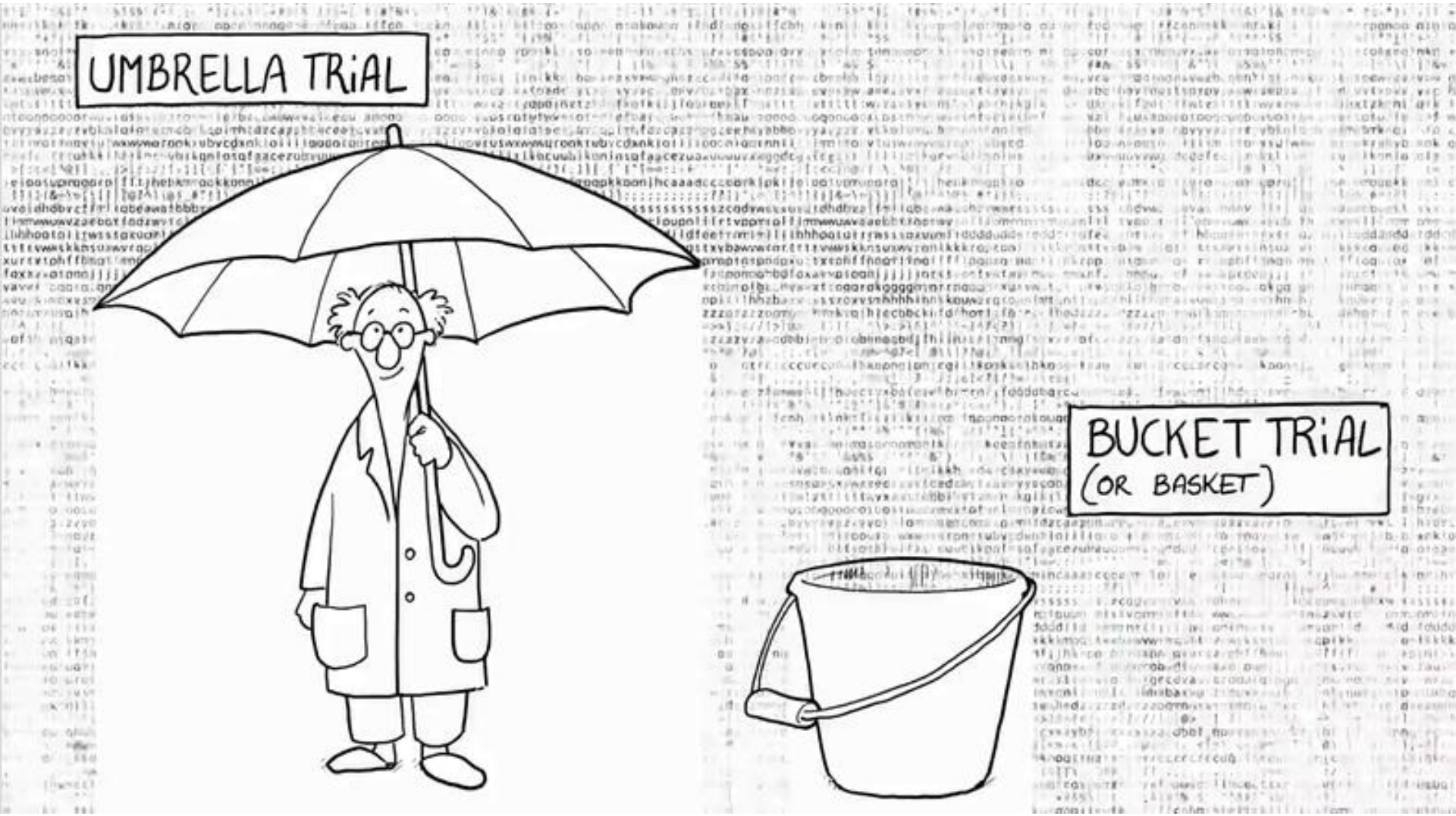
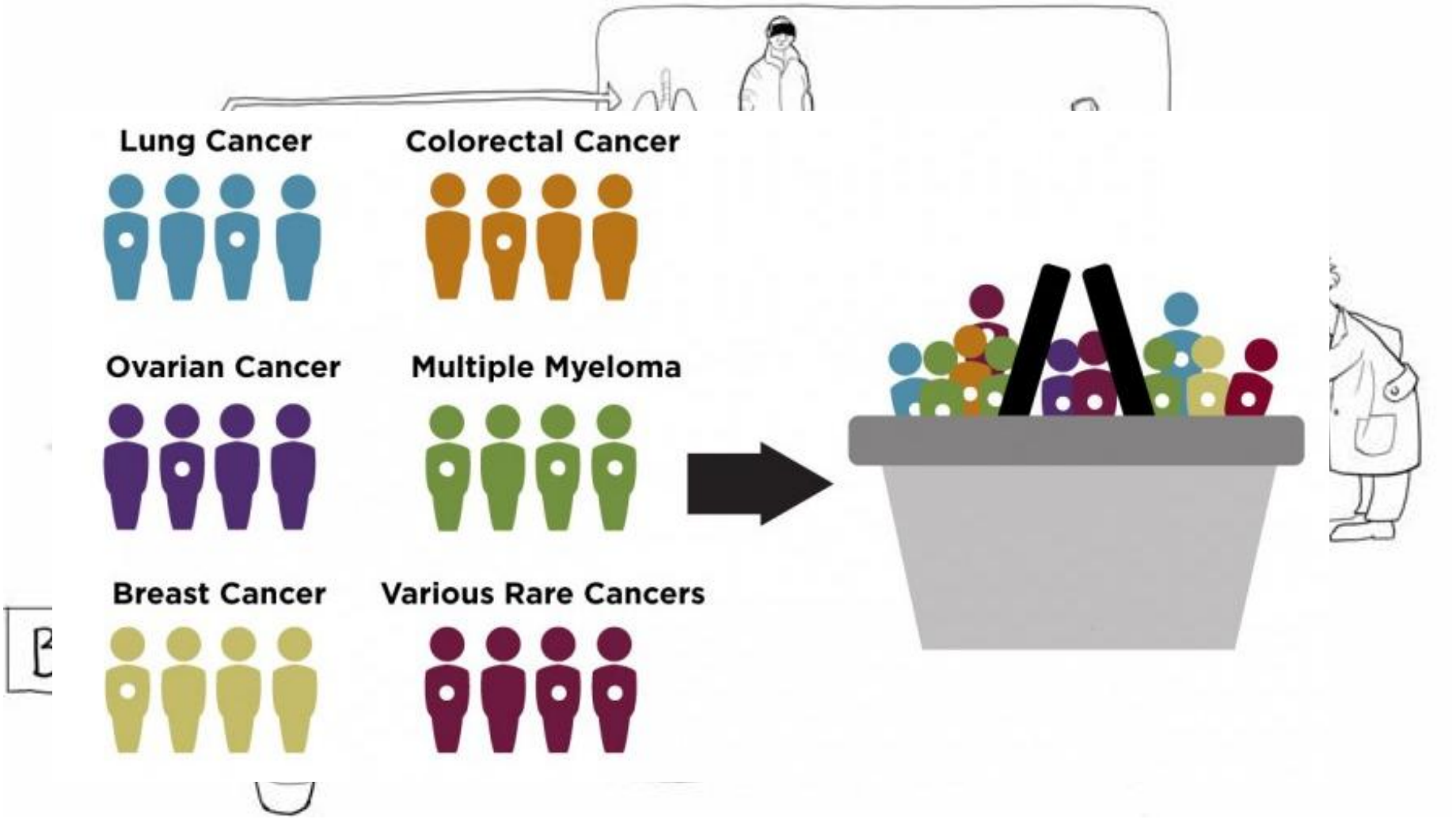
✓ Understanding the molecular biology of cancer
✓ Innovations in drug development technology
✓ Translation of these findings into effective cancer treatment
New era of new clinical trials

New era of new clinical trials



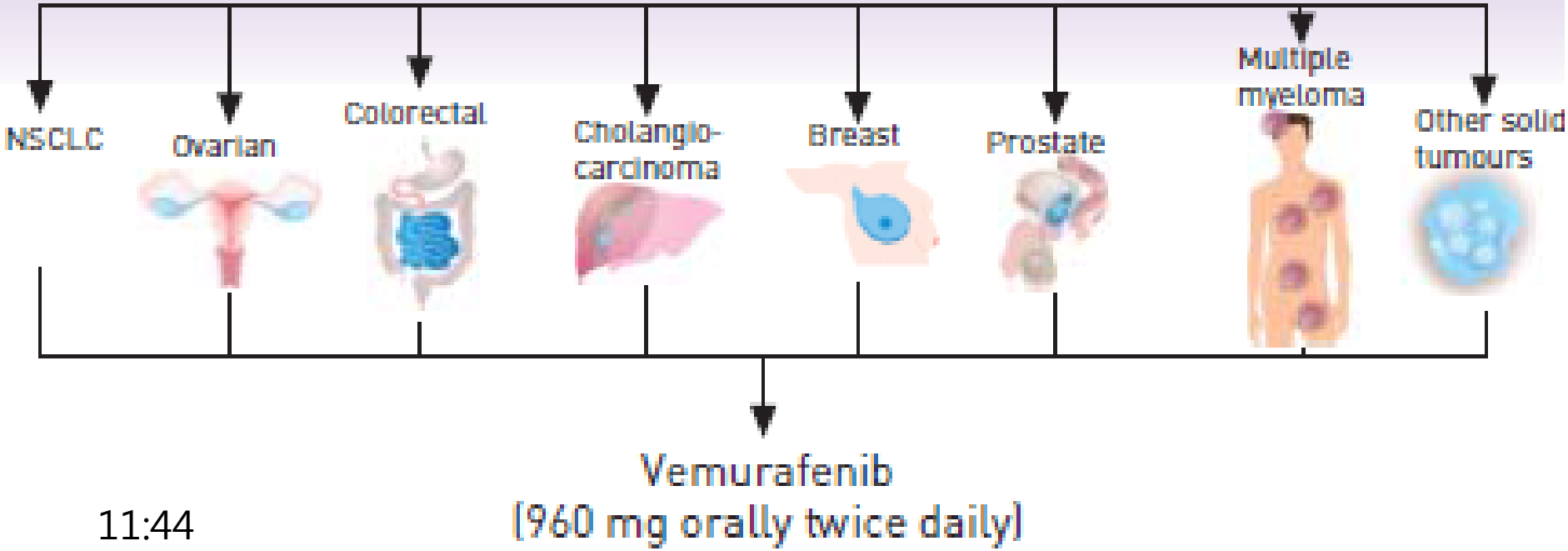
Basket Trial ; One drug - multiple disease



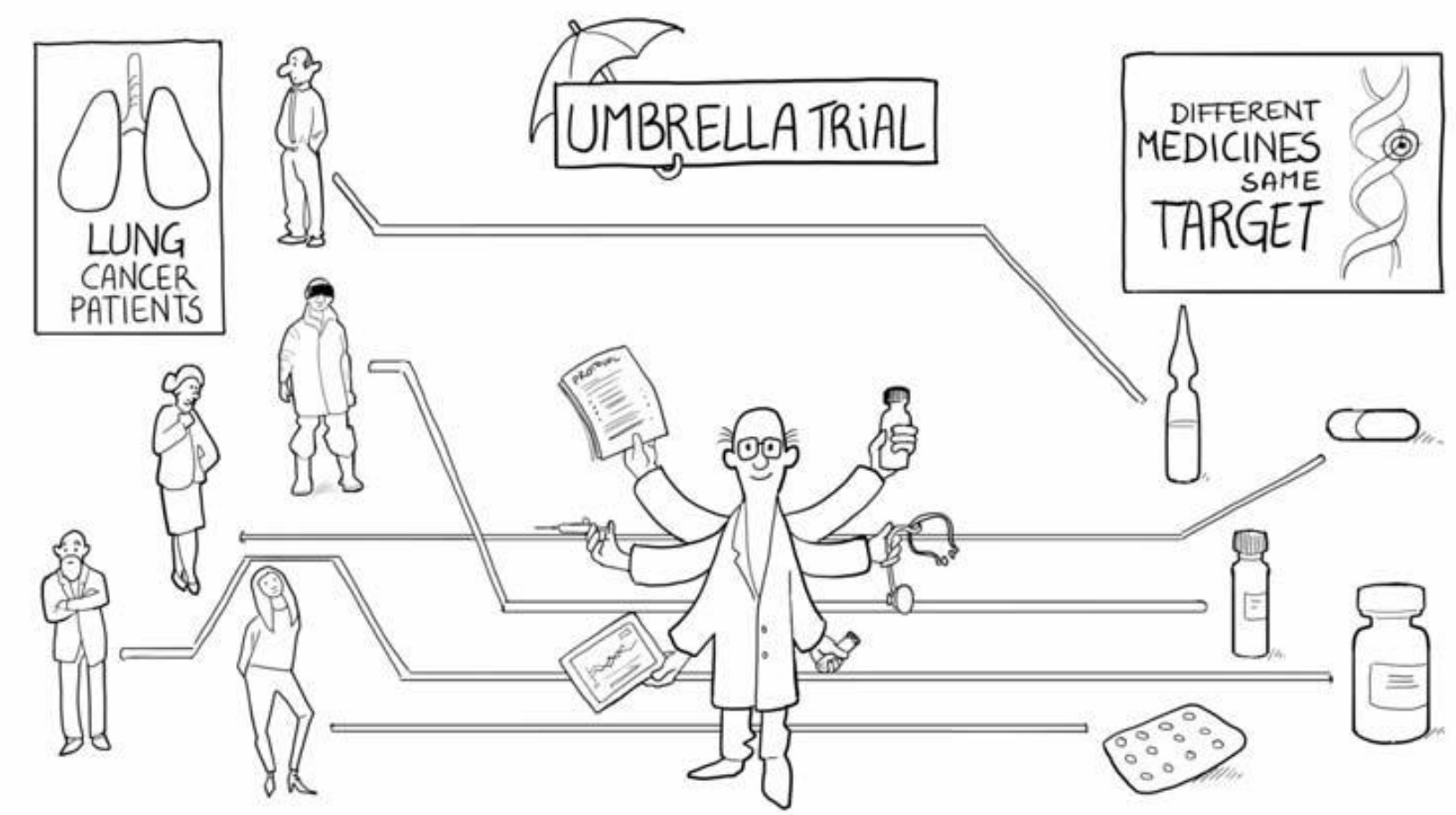
Basket Trial ; One drug - multiple disease

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



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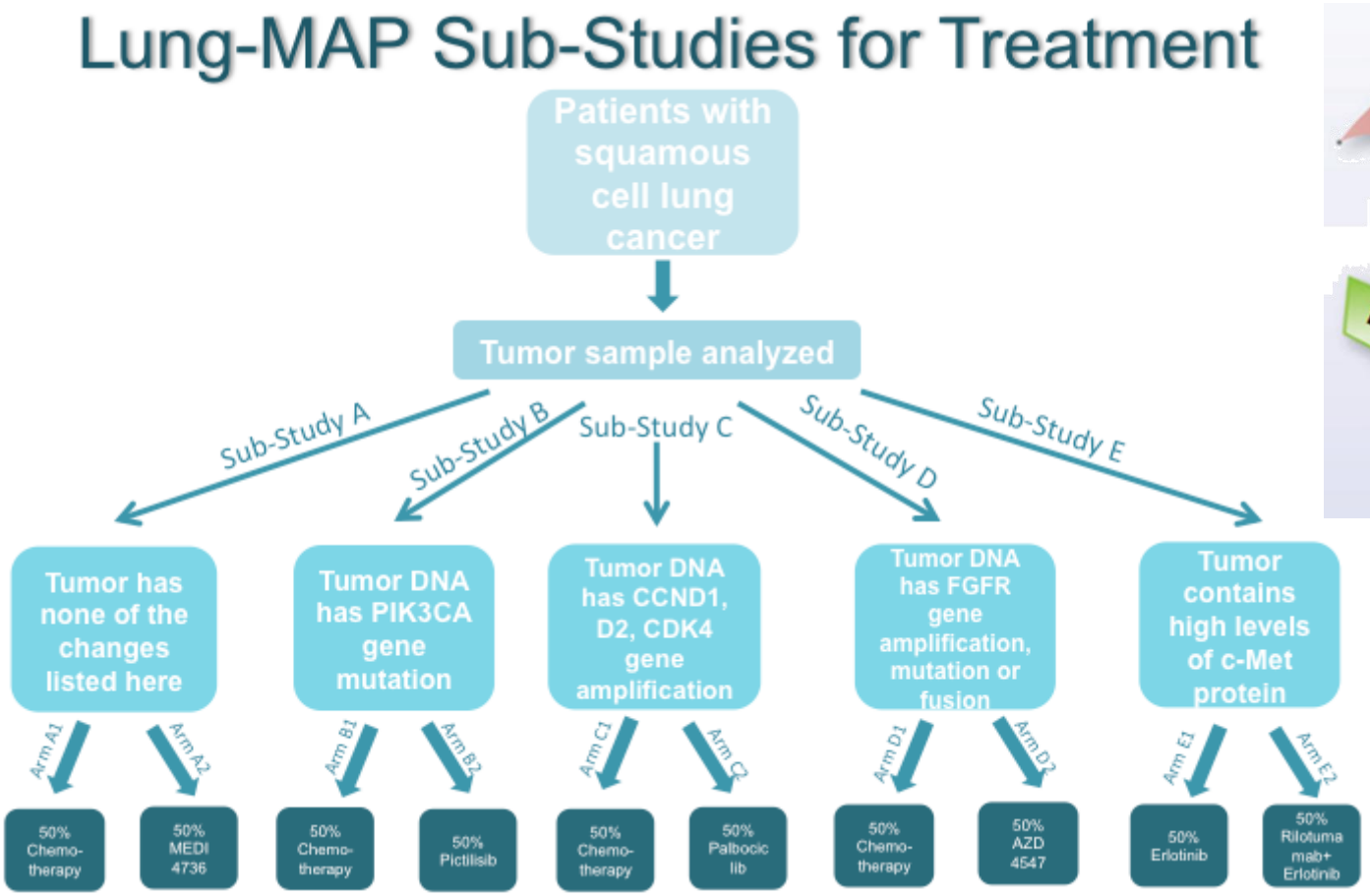
Umbrella Trial

하나의 질병에 대해 여러 가지 약물의 효능을 테스트하는 임상



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Umbrella Trial의 실제

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Ongoing Umbrella Trials

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

CANCER DISCOVERY 2011

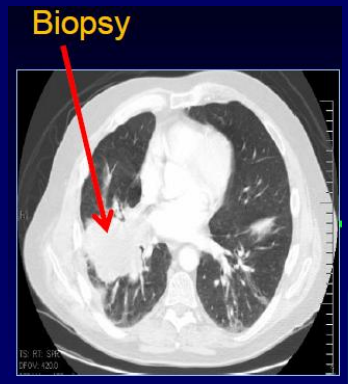
Enrollment into BATTLE-1 Umbrella Protocol

Activated

Eligibility

Prior chemotherapy

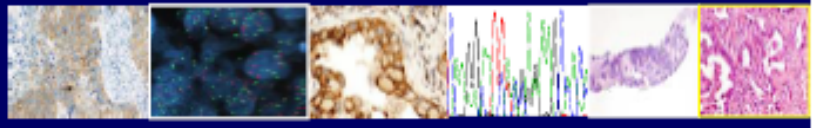
Biopsiable disease



Core Biopsy

Biomarker Assessment

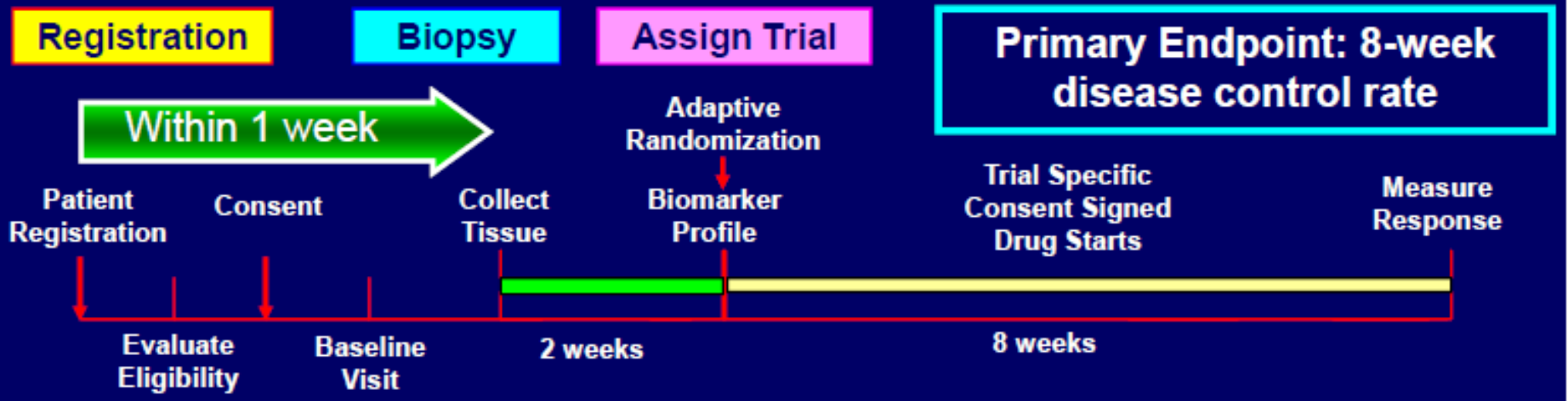
1. EGFR mutation
2. EGFR Increased copy number
3. KRAS mutation
4. BRAF mutation
5. VEGF expression
6. VEGFR-2 expression
7. RXRa expression
8. RXRb expression
9. RXRg expression
10. Cyclin D1 expression
11. Cyclin D1 amplification

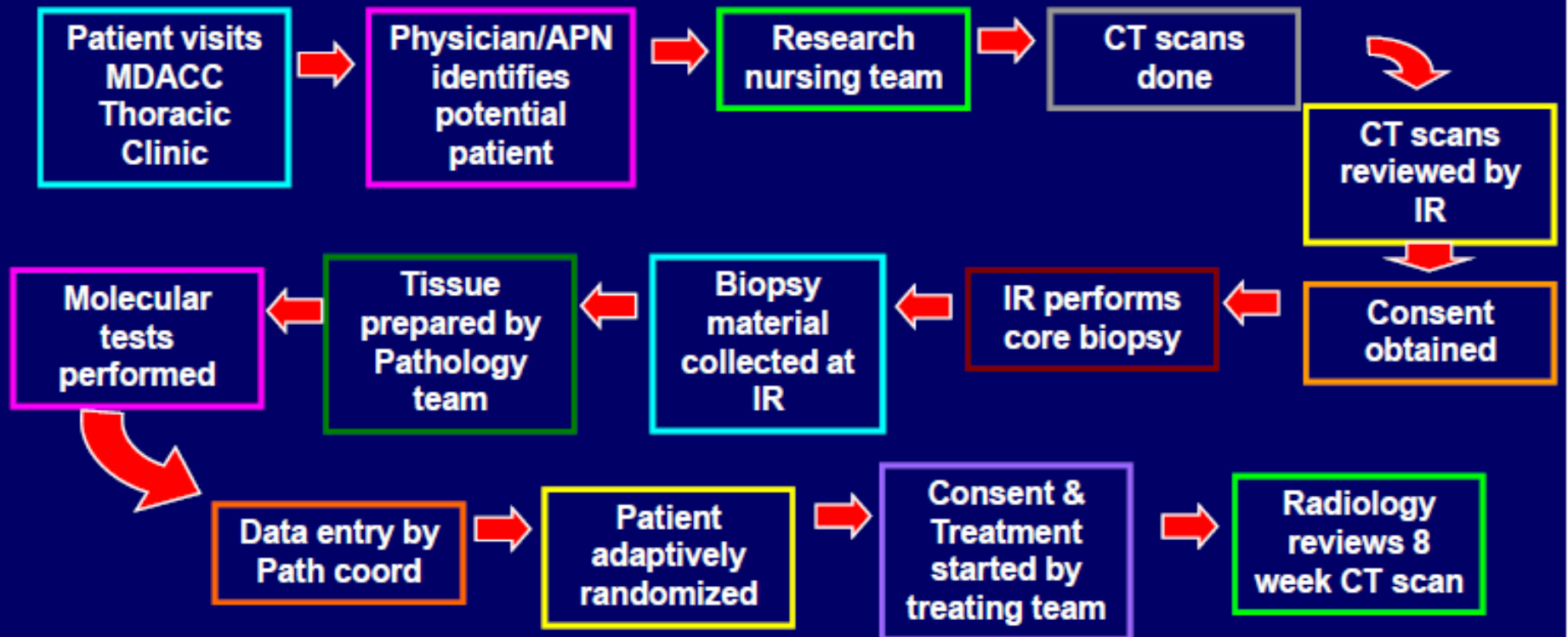


Biomarker Profile and Adaptive Randomization

EGFR	Ras/Raf	VEGF	CycD1/RXR
Erlotinib	Sorafenib	Vandetanib	Erlotinib + Bexarotene

BATTLE-1 Workflow



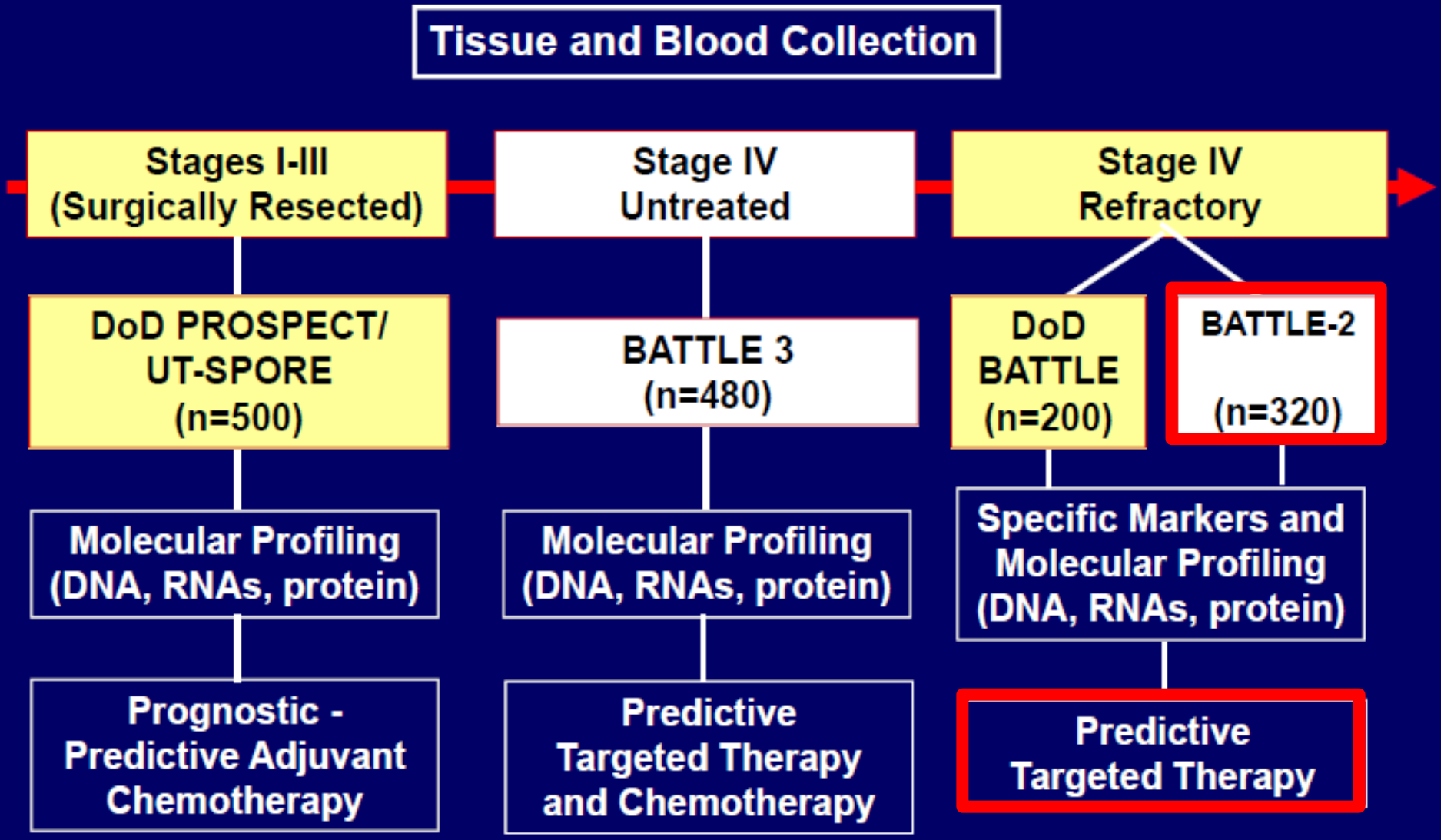


BATTLE Results: Disease Control in % (n)

Treatments	Marker Groups					Total
	EGFR	*KRAS*	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)

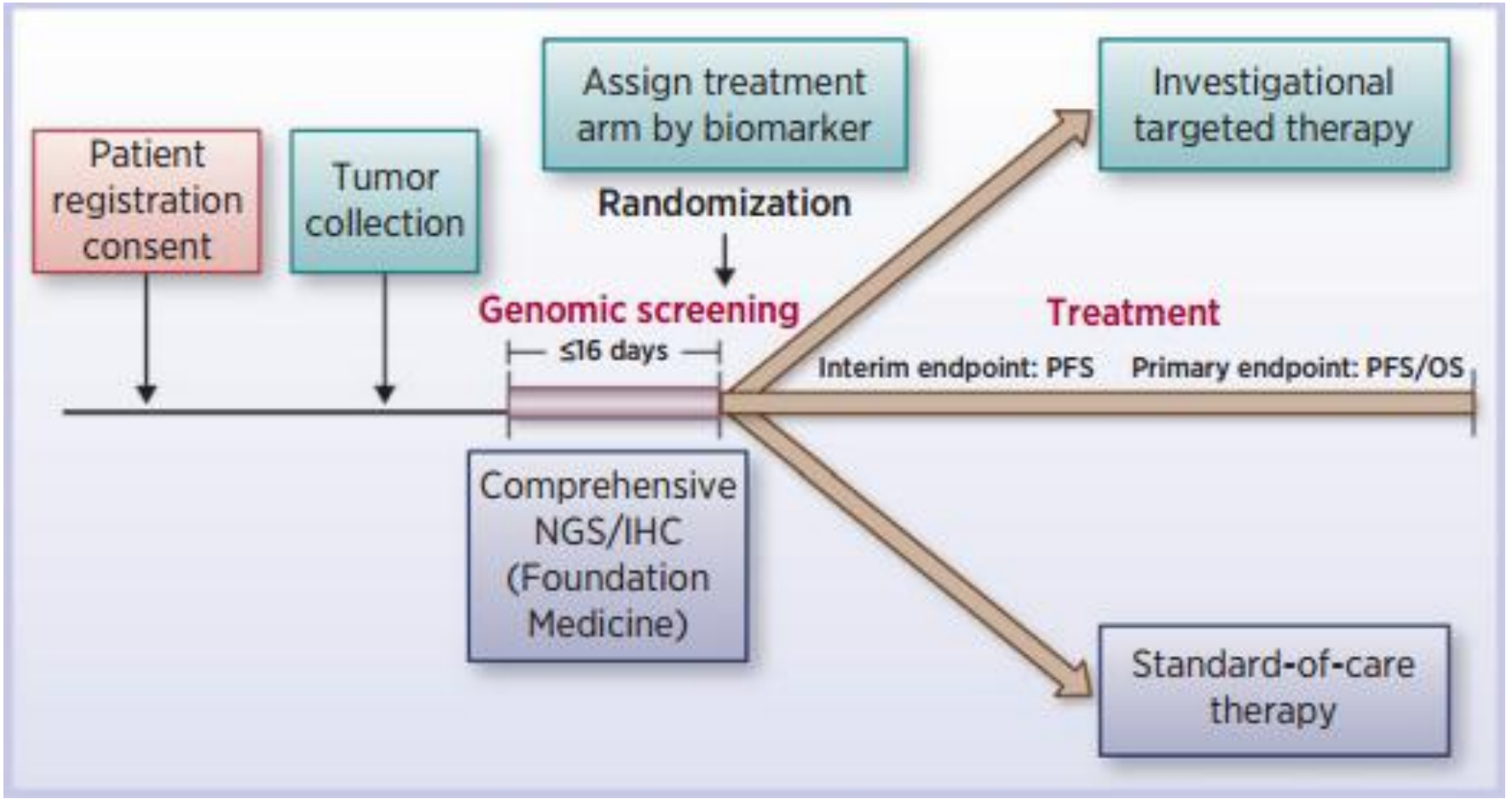
MD Anderson Lung Cancer Program

Personalized Therapy Strategy in NSCLC



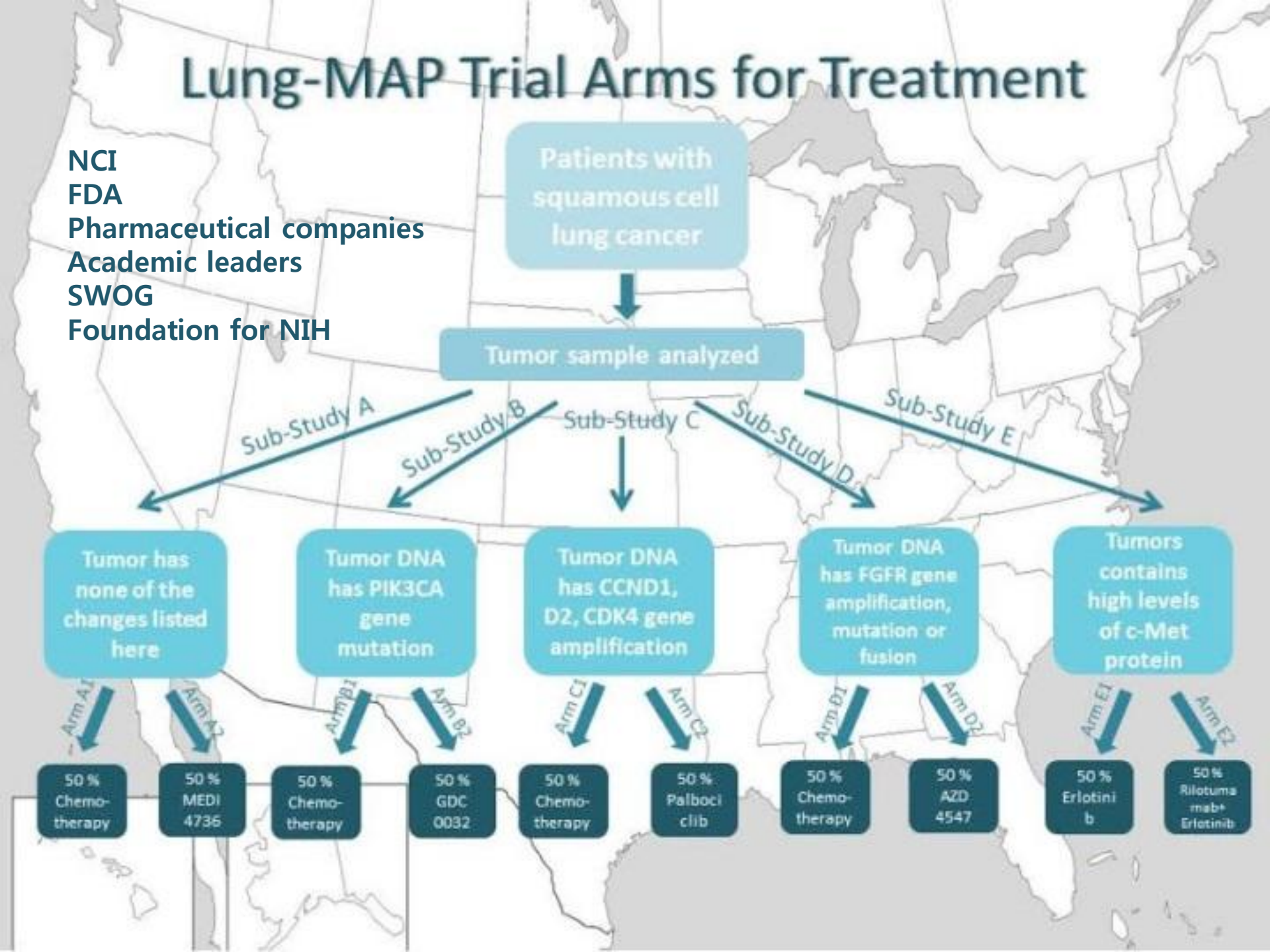
Clinical Cancer Research

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

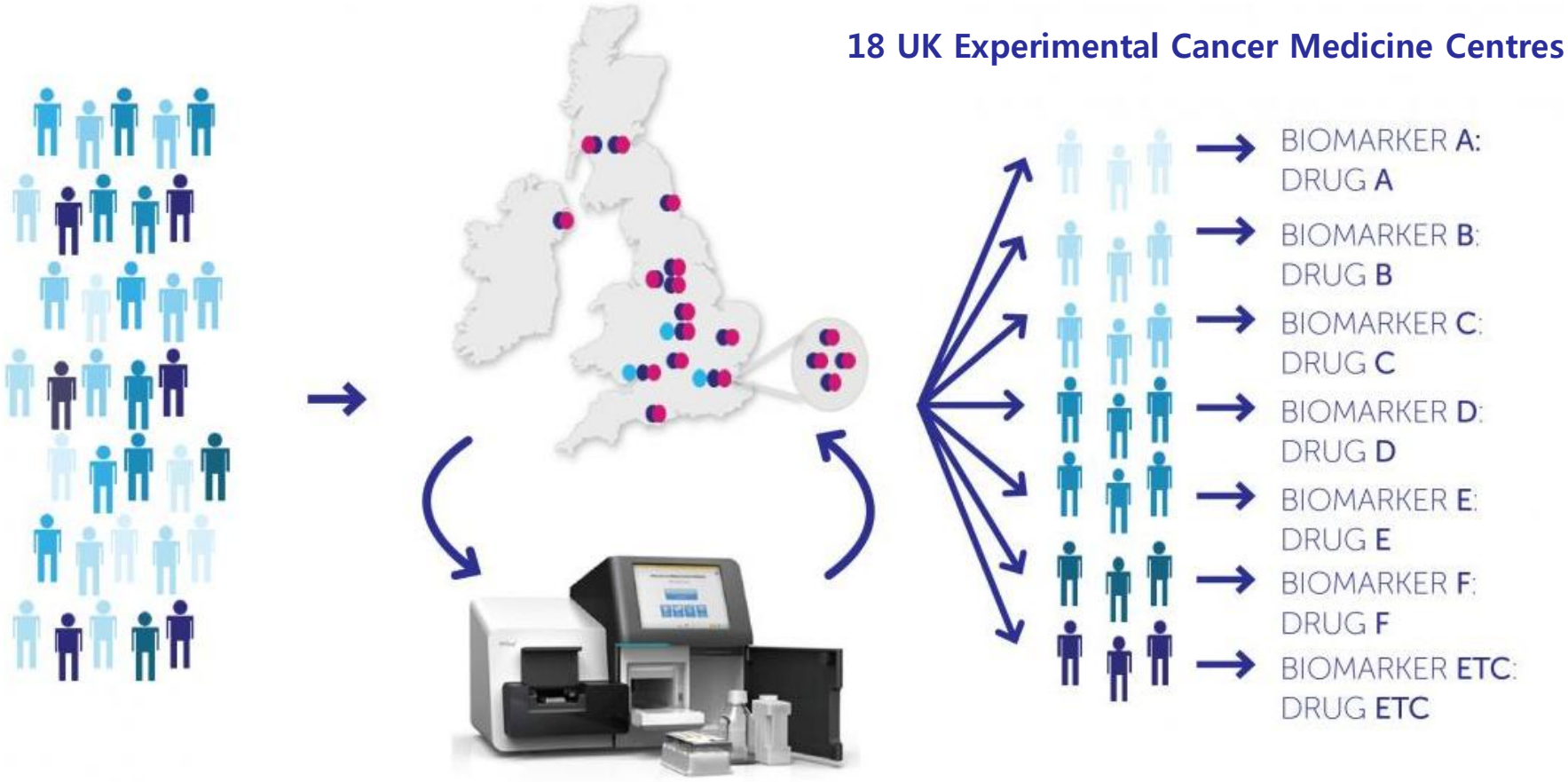


Lung-MAP Trial Arms for Treatment

NCI
FDA
Pharmaceutical companies
Academic leaders
SWOG
Foundation for NIH



National Lung Matrix Trial



AstraZeneca/MedImmune
Pfizer

PRE-SCREENING

NGS SEQUENCING

MATRIX LUNG STUDY

Molecular cohorts and initial estimated prevalence rates		AZD4547 Arm A	AZD2014 Arm B	Palbociclib Arm C	Crizotinib Arm D	Selumetinib + docetaxel Arm E	AZD5363 Arm F	AZD9291 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 Identificaiton and Sequencing Trial)

Prior studies of adjuvant targeted therapies in NSCLC

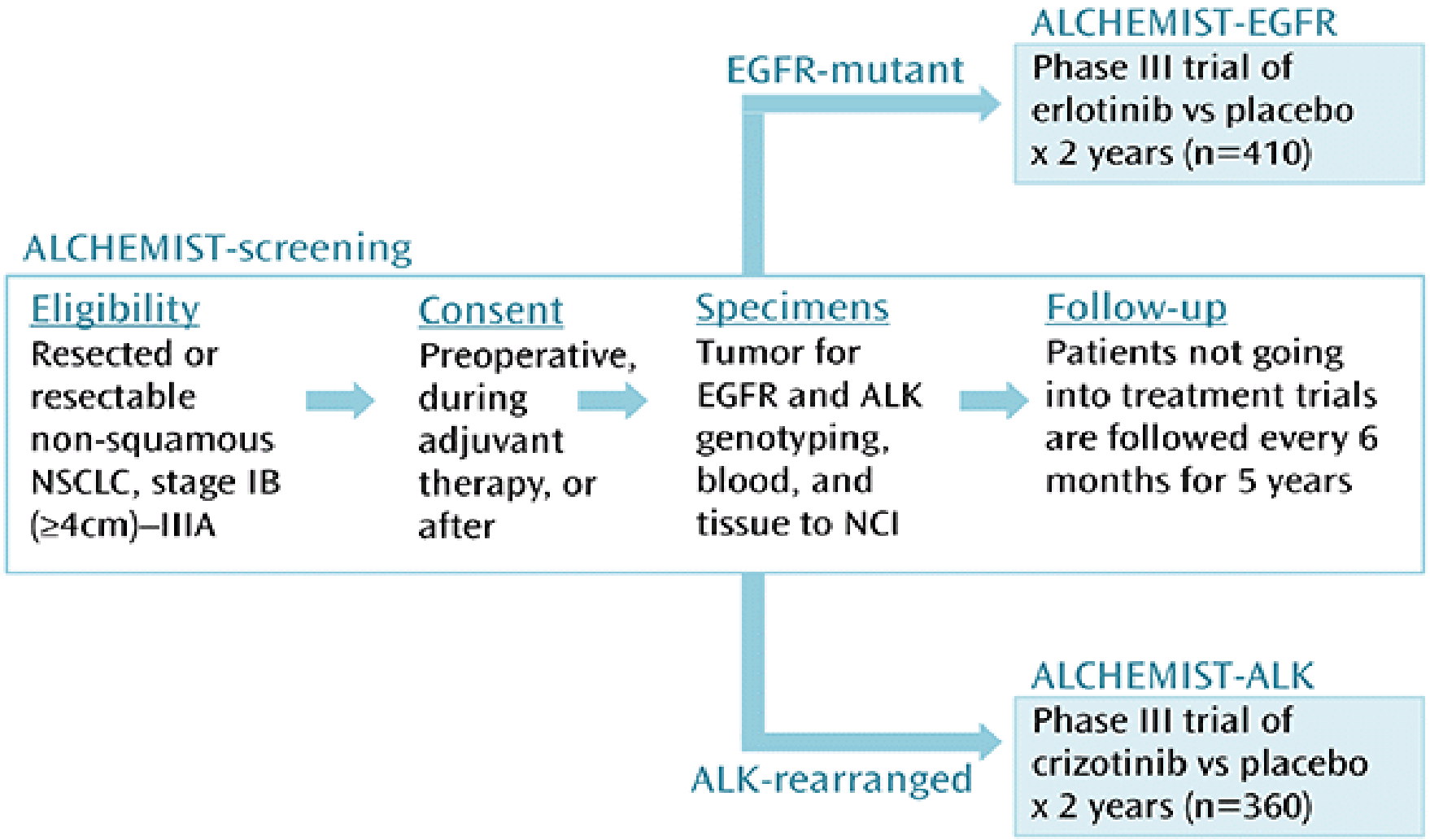
Trial	Disease	Treatment	Exposure	Primary endpoint	DFS	OS
NCIC CTG BR.19 trial (21)	NSCLC, no molecular selection	Gefitinib *vs.* placebo (1:1)	2 years	OS	HR 1.22 (0.93- median 6.3 yea 2%	1.24 (0.94-1.64) P=0.14; median 5.1 years ; at 6.3 years, 54%
RADIANT trial (22)	NSCLC, EGFR+ by IHC or FISH	Erlotinib *vs.* placebo (2:1)	2 years	DFS	HR 0.90 (0.74-1. median 50.5 48.2 months	s (0.88-1.45) P=0.3350
D'Angelo *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

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

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

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™)

  BRAF억제제 다브라페닙(dabrafenib, Tafinlar)

  MEK 억제제 트라메티닙(trametinib, Mekinist)

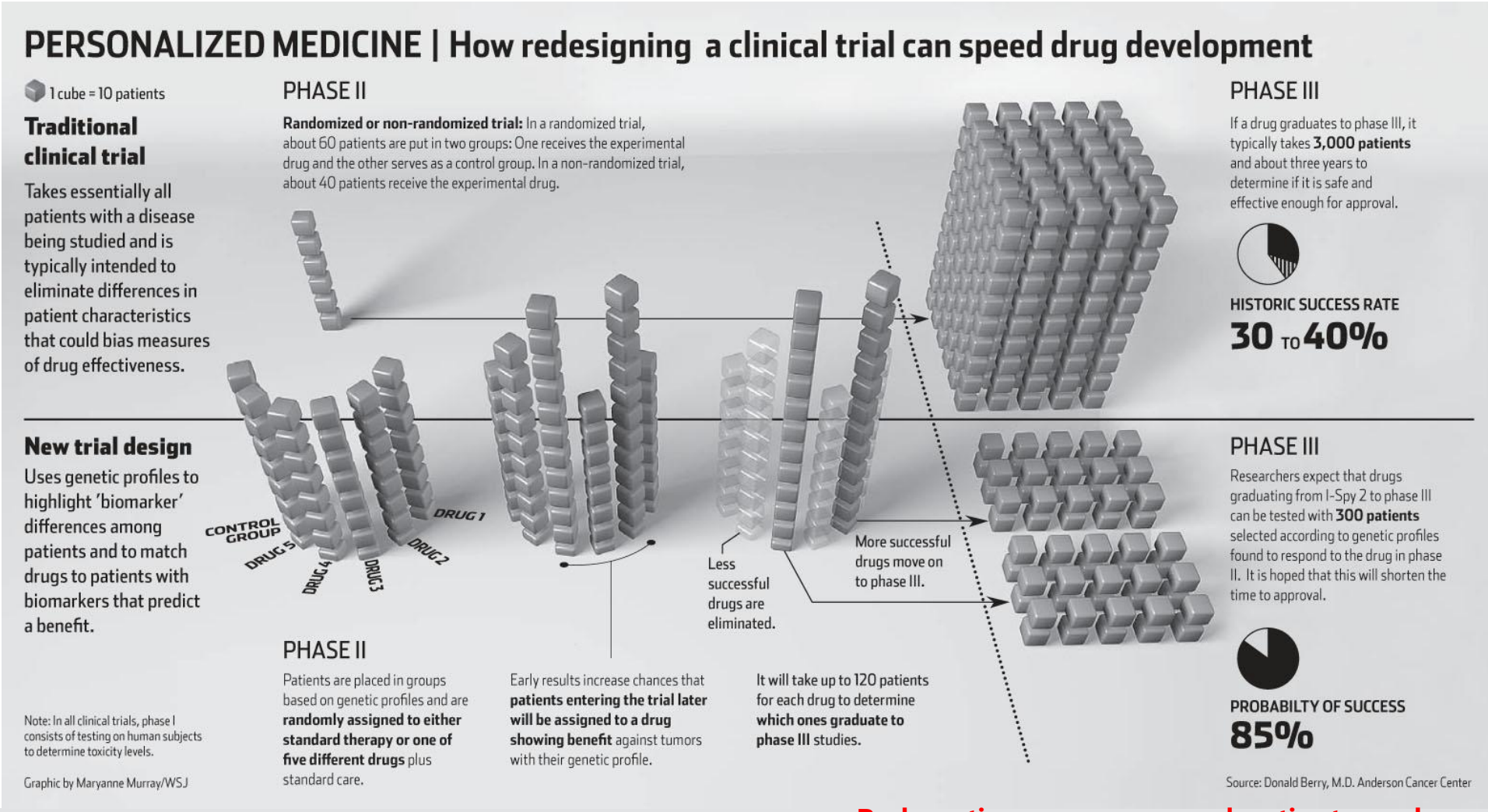
  EGFR 억제제 EGF816

  C-Met 억제제 INC280

  면역항암제 PDR001(anti-PD-1 Monoclonal Ab, Novartis)

11:44

새로운 임상연구 디자인의 장점

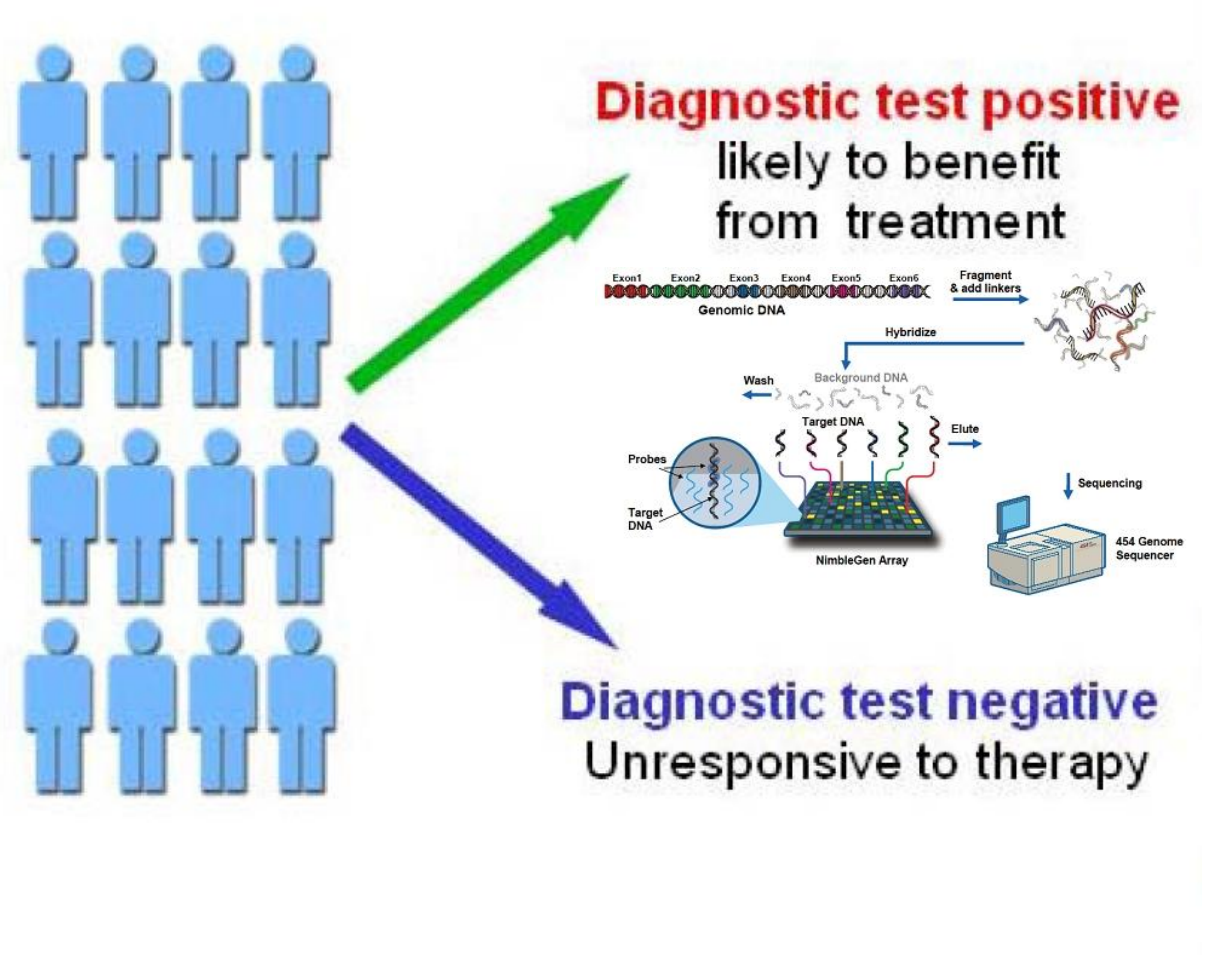


Reduce time, resource, and patient numbers

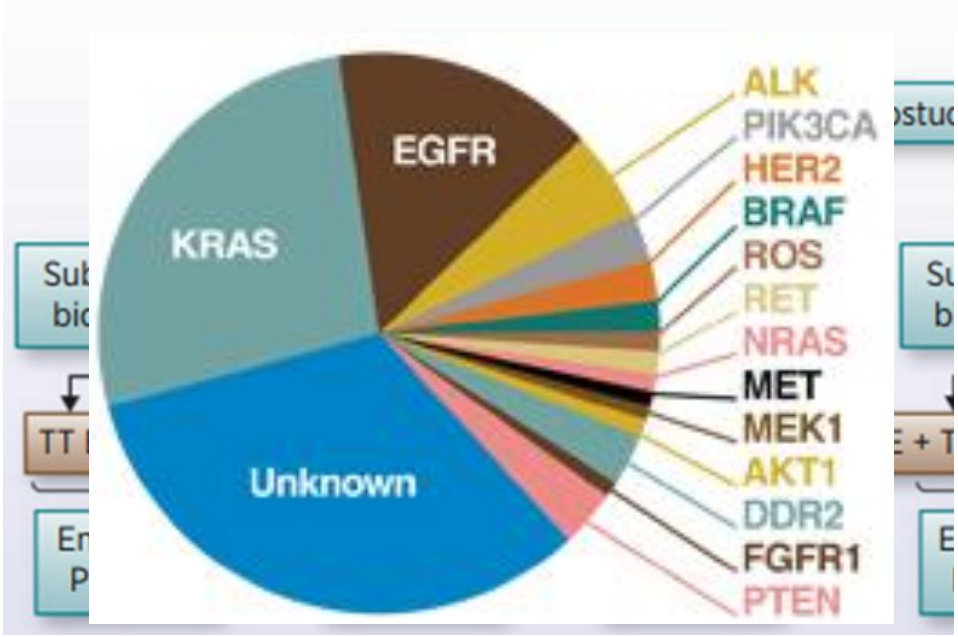
11:44

Umbrella Trial 성공의 필요조건

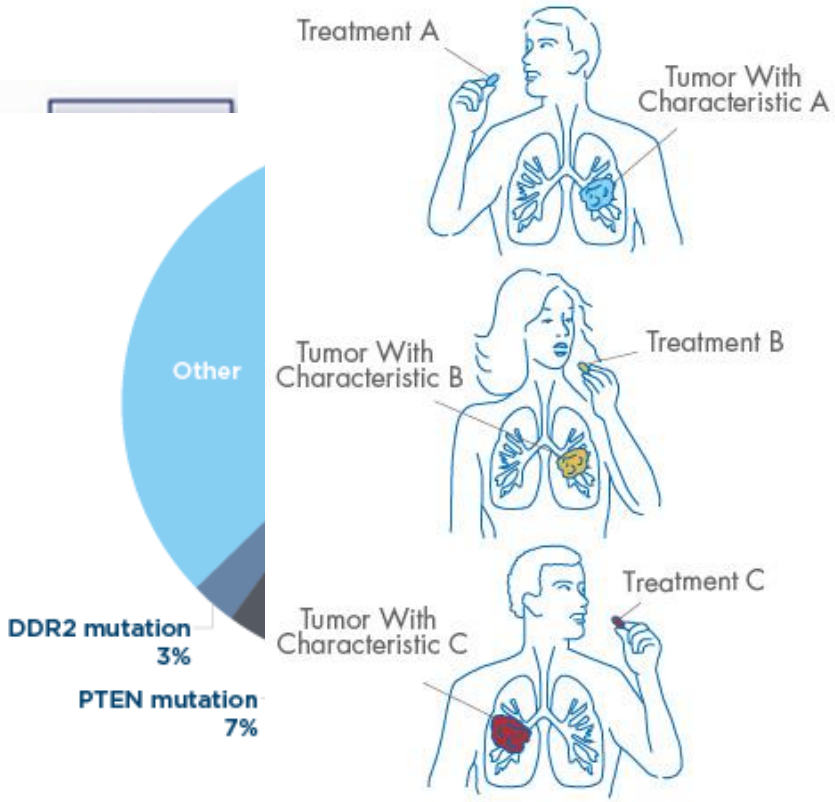
맞춤의료의 시대와 새로운 디자인의 임상시험



맞춤의료의 시대와 새로운 디자인의 임상시험



Adenocarcinoma



Squamous cell carcinoma

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성공적인 Umbrella trial 의 필수조건

Clinicians, IT personal, project managers, drug providers, biostatistician, 정부기관 등의 유기적인 협조가 필요함.

결 론

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	Selumetinib + docetaxel	AZD5363	AZD9291
		Arm D	Arm E	Arm F	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%				