

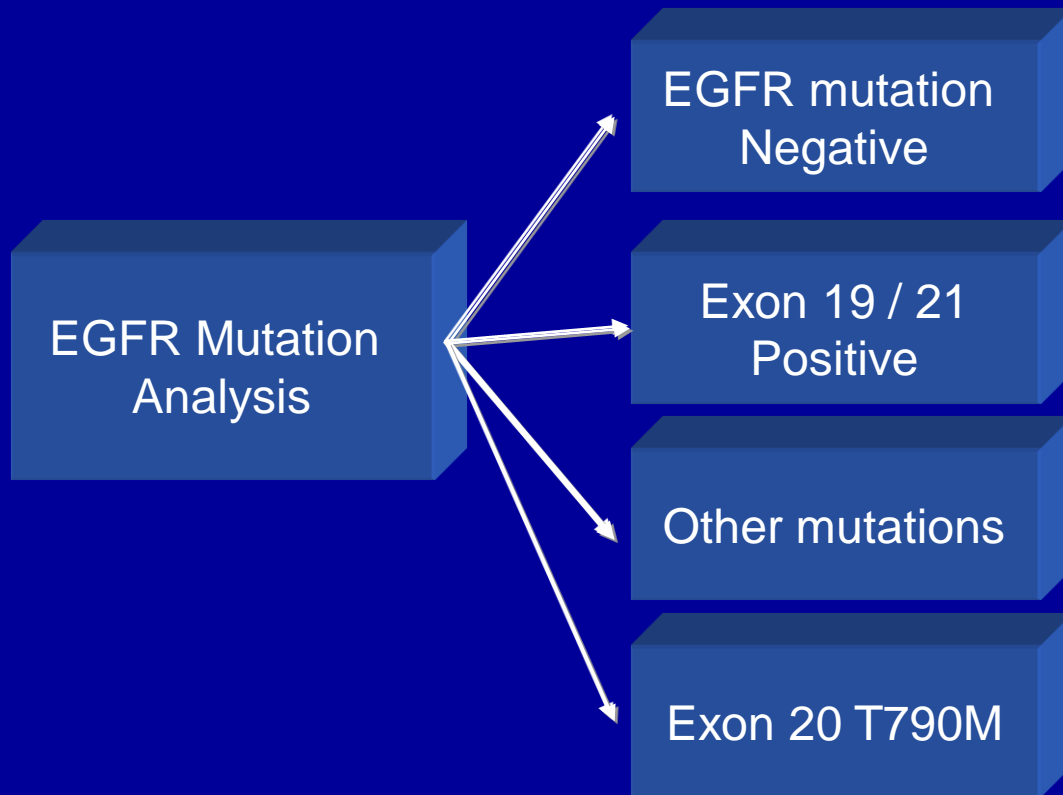
EGFR TKI First-line Therapy: Diagnostic Assessment and Drug Selection

Professor Tony Mok

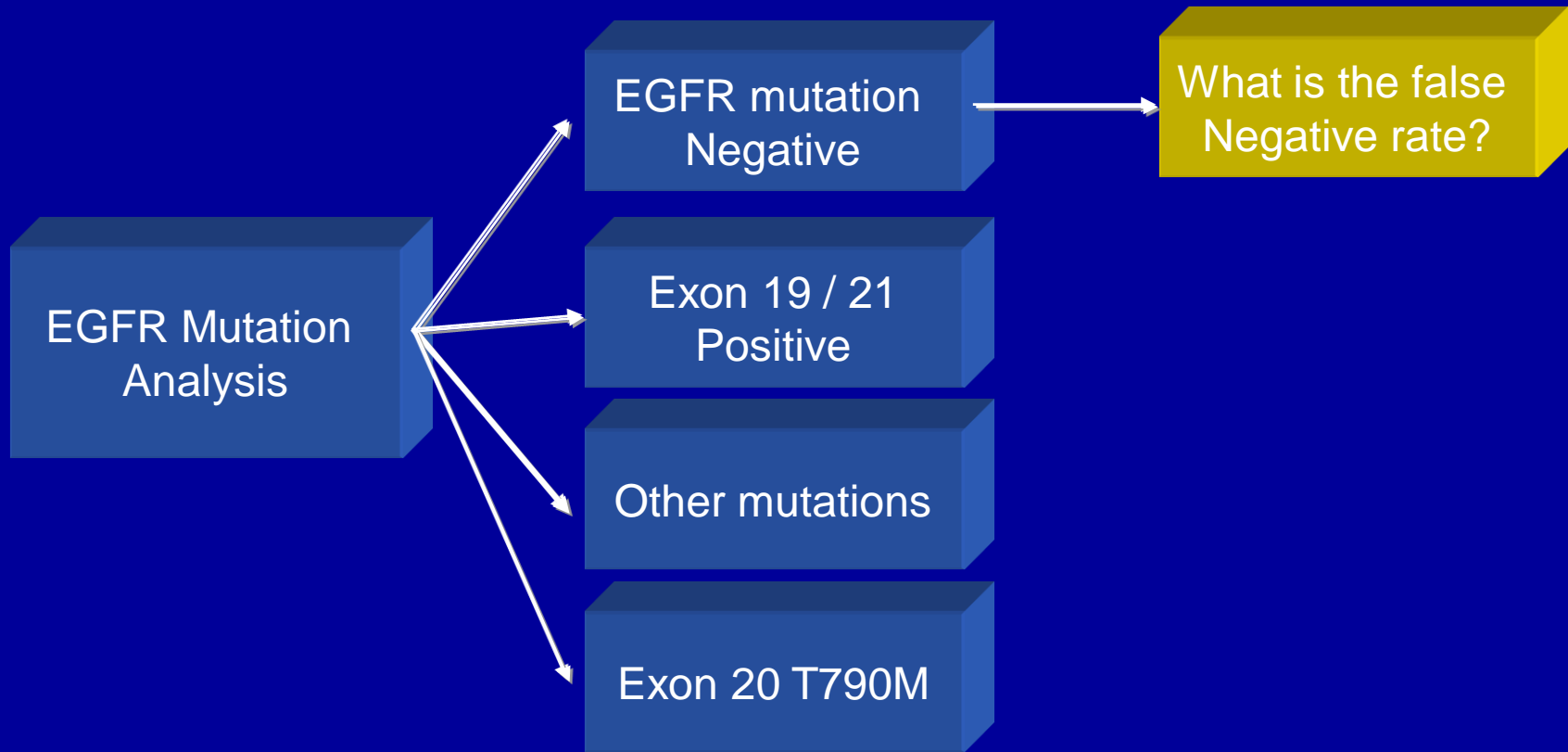
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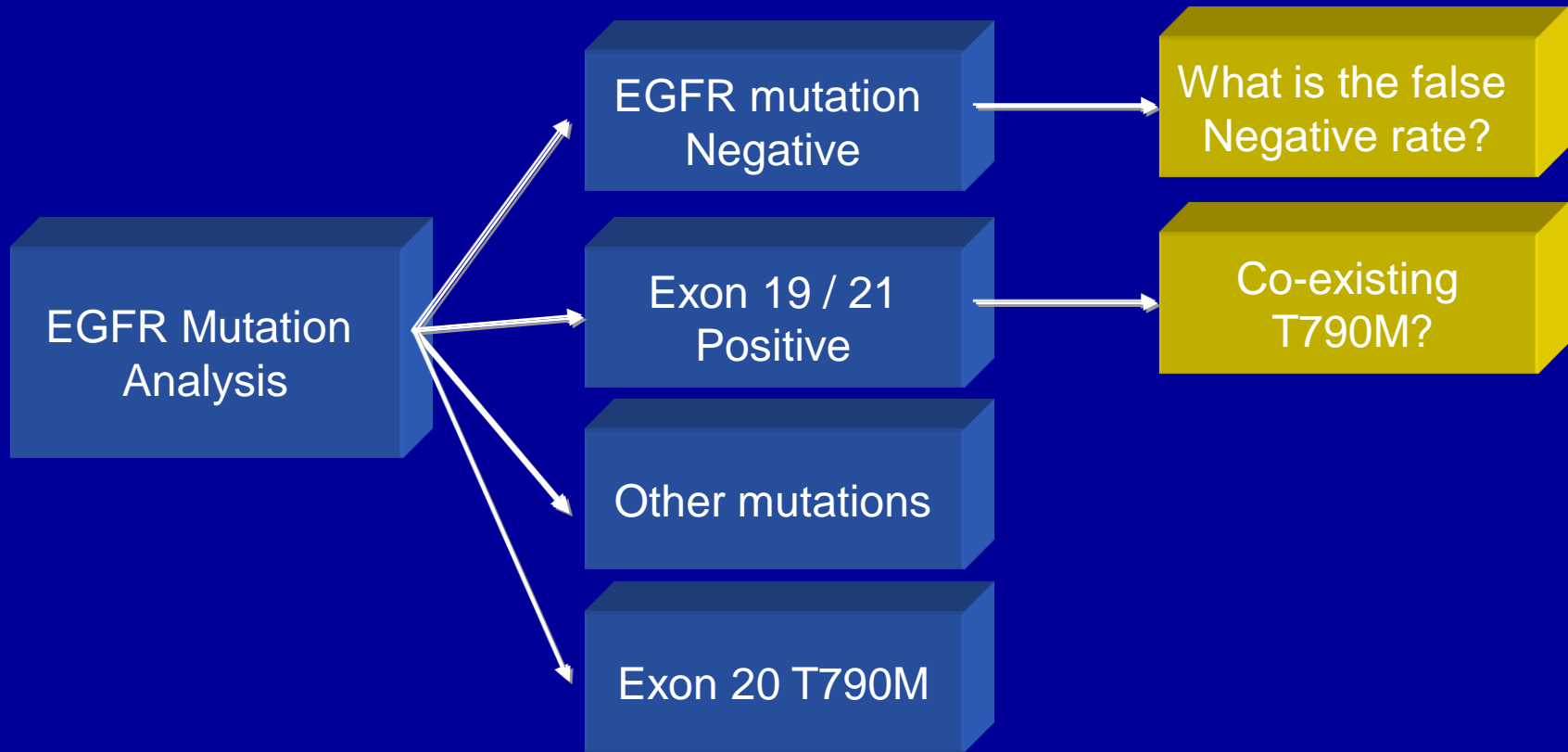
Diagnostic Assessment



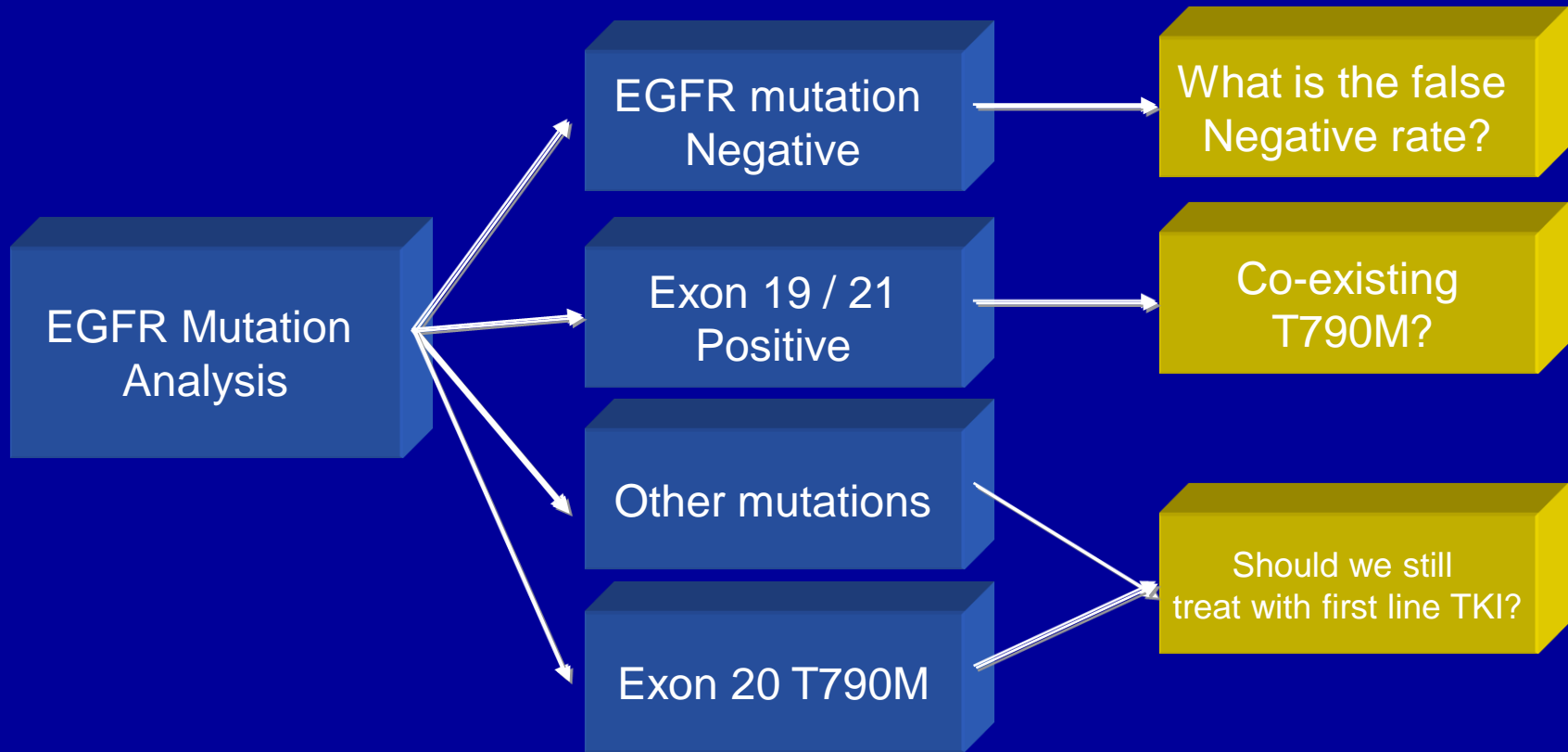
Diagnostic Assessment



Diagnostic Assessment



Diagnostic Assessment



Testing Methods

Pao and Ladanyi, Clin Cancer Res., 2007

Method	Sensitivity (%)	Mutation	Del ins comprehensive analysis
Direct sequencing	25	Known, Unknown	Yes
PCR-SSCP	10	Known, Unknown	Yes
TaqmanPCR	10	Known only	No
Loop hybrid motility shift assay	7.5	Known only	Yes
Cycleave PCR	5	Known only	No
PCR-RFLP	5	Known only	No
Length (fragment)analysis	5		Yes
MALDI-TOF based(sequenom)	5	Known only	No
PNA-LNA PCR clamp	1	Known only	No
Scorpion ARMS	1	Known only	No
dHPLC	1	Known, Unknown	Yes
Single molecule sequencing	0.2	Known, Unknown	Yes
Mutant enriched PCR	0.2	Known only	No
SMAP	0.1	Known only	No

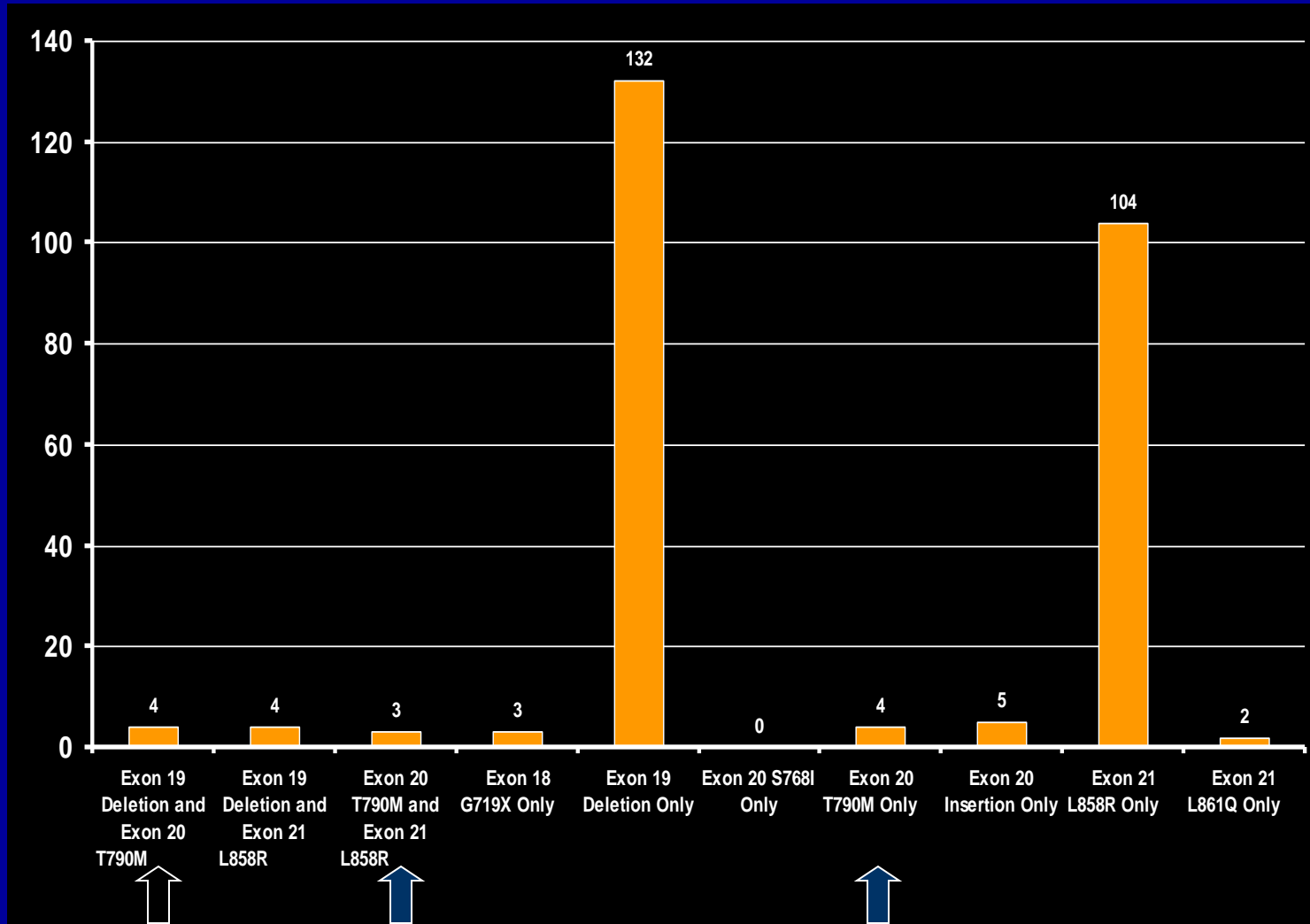
First-SIGNAL: Comparison of ORR by EGFR Mutation Status

Variables	Positive (N=42)		Negative (N=54)	
	Gefitinib (N=26)	GP (N=16)	Gefitinib (N=27)	GP (N=27)
ORR (CR+PR)	22 (84.6%)	6 (37.5%)	7 (25.9%)	14 (51.9%)
Odds Ratio (95% CI)	9.167 [2.109, 39.847]		0.325 [0.103, 1.021]	
P-value	0.002		0.051	
DCR (CR+PR+SD)	23 (88.5%)	16 (100.0)	11 (40.7%)	22 (81.5%)
Odds Ratio (95% CI)	NE		0.156 [0.045, 0.539]	
P-value	0.275		0.002	

Not all EGFR mu –ive patients are truly EGFR mu –ive. Testing method and quality of sample should be reviewed.

T790M mutation in IPASS

- 11 patients in the IPASS study were found to harbour the T790M mutation in the EGFR gene



Treatment naïve patients with T790M mutation

Gefitinib

- 5 patients with the T790M mutation
 - 3 of these patients (E1704005, E1706001, E7001001) had a partial response (all of these 3 patients also had the Exon 19 deletion mutation)
 - 1 patient (E1705014) with stable disease (also had the L858R mutation)
 - 1 patient (E1706006) with progressive disease at the first post-baseline scan (this patient only had the T790M mutation).

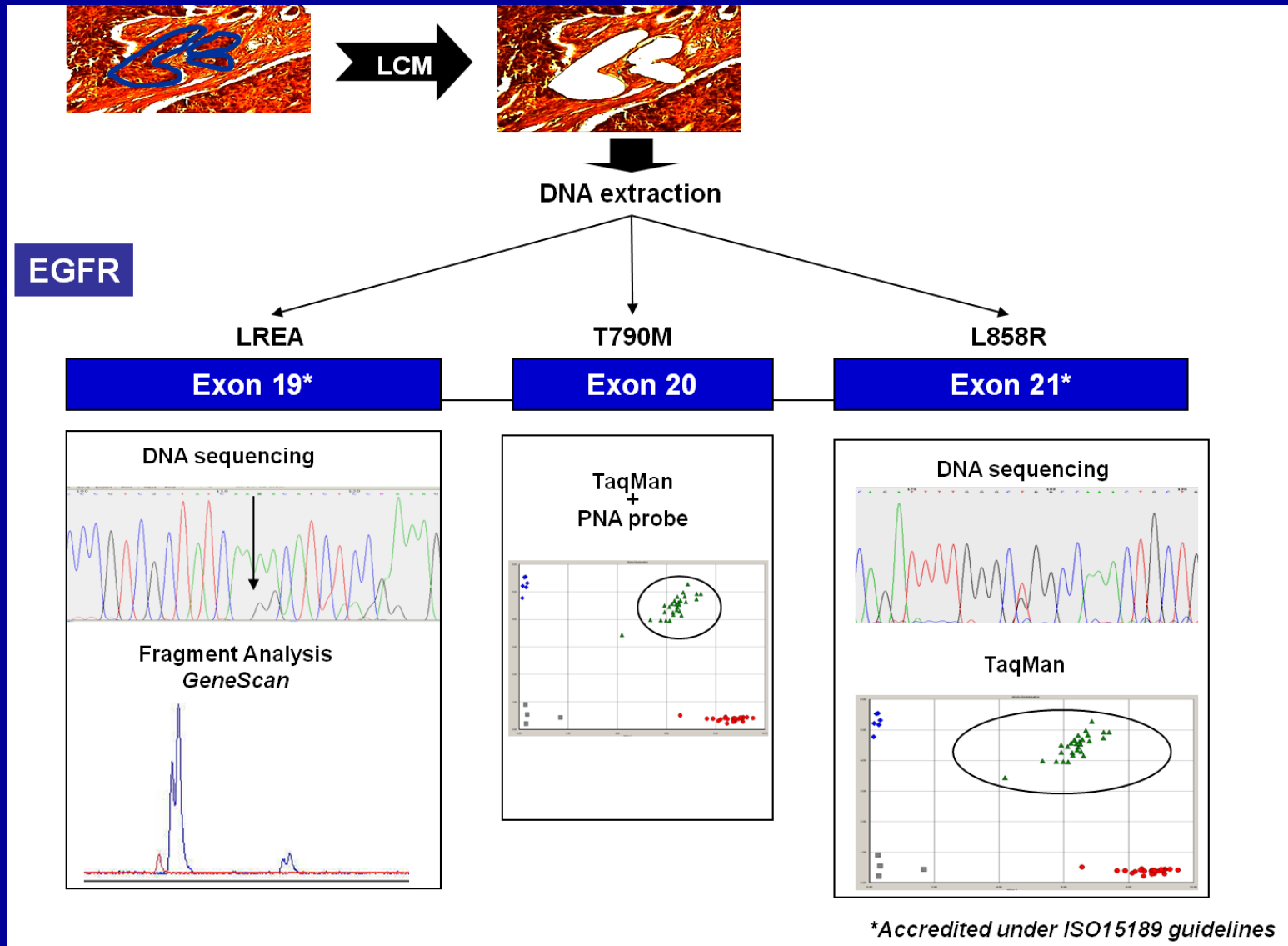
Carboplatin/Paclitaxel

- 6 patients with the T790M mutation
 - 3 of these patients had a partial response (1 (E0839001) also had the L858R mutation, 1 (E5208006) also had the Exon 19 deletion mutation and 1 (E5208011) only had the T790M mutation)
 - 2 patients (E0849003, E1406025) with stable disease (both of these only had the T790M mutation)
 - 1 patient (E7001004) with progressive disease at the first post-baseline scan (this patient also had the L858R mutation)

Sensitivity of T790M testing

Sample ID	Treatment Arm	Status	Mutation Status - Genzyme		ME-PCR	RDG DNA ARMS Mutant	Genzyme DNA ARMS Mutant	Sequencing
			T790M	L858R				
E0839001	Carboplatin/Paclitaxel	PR	T790M	L858R	Yes	Yes	Yes	Yes
E0849003	Carboplatin/Paclitaxel	SD	T790M	no other	N	No	No	No
E1704005	Gefitinib	PR	T790M	Ex 19	N	Brdline?	No	No
E1706001	Gefitinib	PR	T790M	Ex 19	Failed	Brdline?	No	No
E5208006	Carboplatin/Paclitaxel	PR	T790M	Ex 19	Yes	Brdline?	No	No
E5208011	Carboplatin/Paclitaxel	PR	T790M	no other	N	No	No	No
E7001001	Gefitinib	PR	T790M	Ex 19	N	No	No	No
E7001004	Carboplatin/Paclitaxel	PD	T790M	L858R	Yes	No	No	No
E1406025	Carboplatin/Paclitaxel	SD	T790M	no other	not analysed			
E1705014	Gefitinib	SD	T790M	L858R	not analysed			
E1706006	Gefitinib	PD	T790M	no other	not analysed			

Spanish Lung Cancer Group

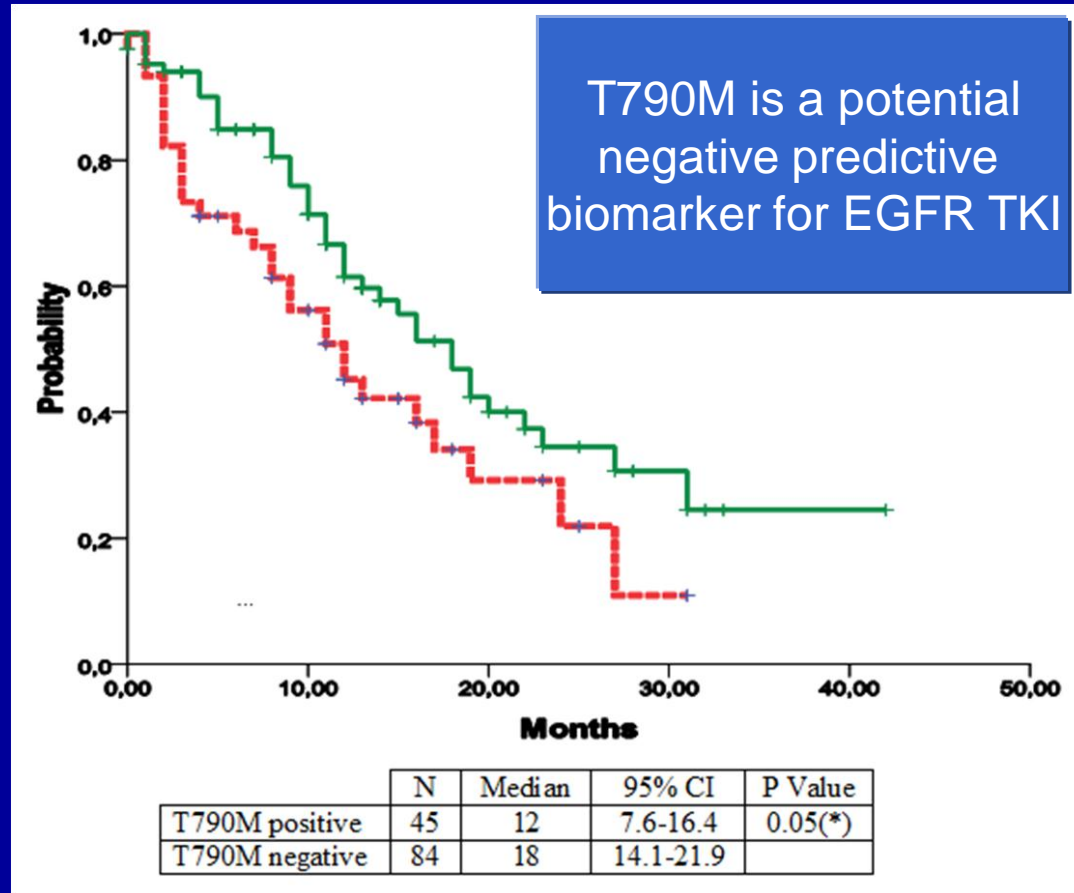


Frequency of T790M

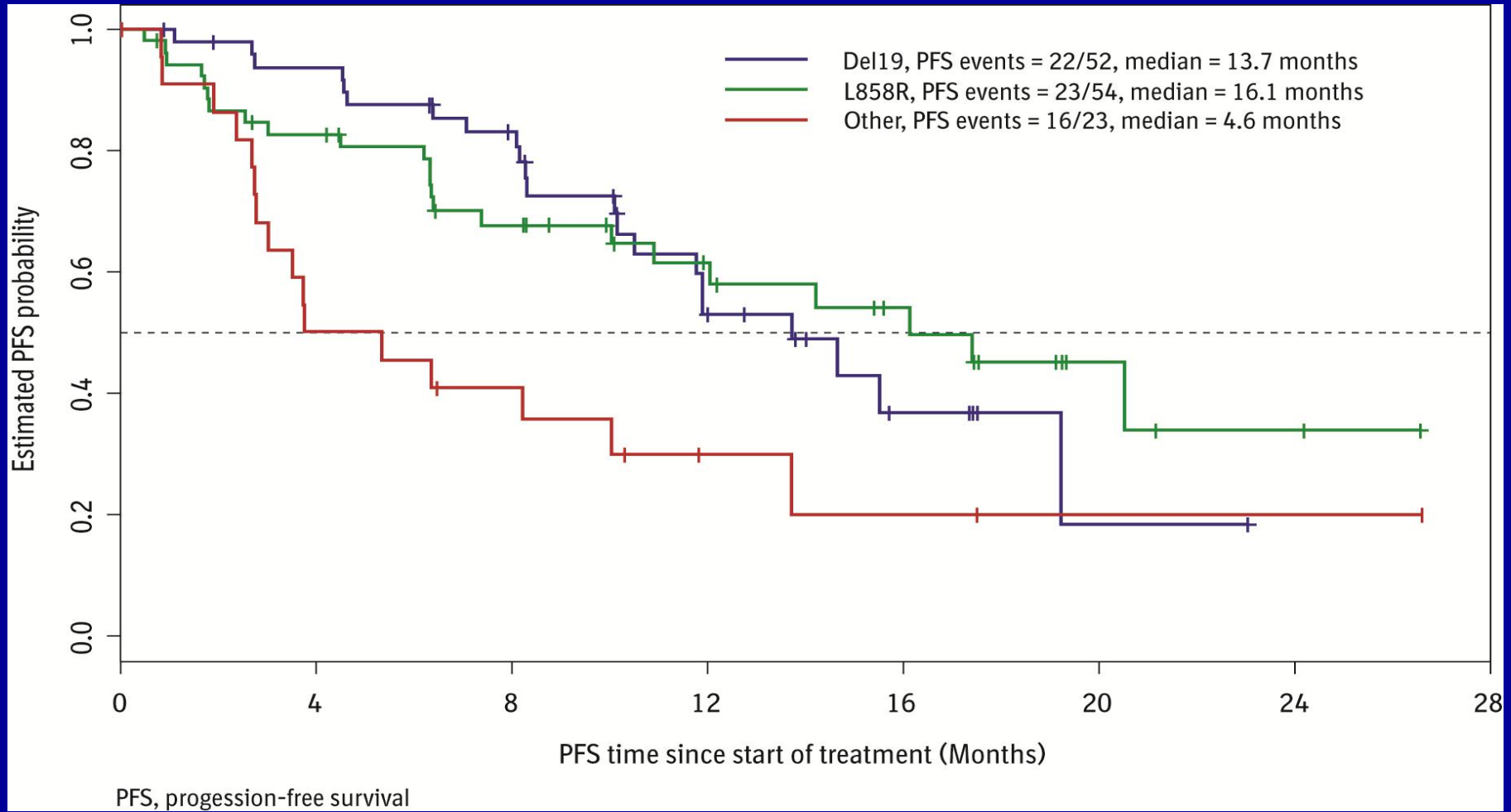
45 out of 129 pts (35%) harbour T790M mutation

	All patients N=129 N (%)	T790M- positive N=45 N (%)	T790M- negative N=84 N (%)	P value
Age, median (range)	67 (22-86)	68 (22-80)	65.5 (35-86)	0.31
Sex				0.31
Male	36 (27.9)	10 (22.2)	26 (31)	
Female	93 (72.1)	35 (77.8)	58 (69)	
Bone metastases				0.03
No	99 (76.7)	29 (64.4)	70 (83.3)	
Yes	30 (23.3)	16 (35.6)	14 (16.7)	
Brain metastases				1
No	116 (89.9)	41 (91.1)	75 (89.3)	
Yes	13 (10.1)	4 (8.9)	9 (10.7)	
Erlotinib therapy				0.58
First-line	65 (50.4)	21 (46.7)	44 (52.4)	
Second-line	64 (49.6)	24 (53.3)	40 (47.6)	
Type of EGFR mutation				0.05
del 19	81 (62.8)	23 (51.1)	58(69)	
L858R	48 (37.2)	22 (48.9)	26(31)	
Response				0.39
Complete or partial response	80 (68.9)	28 (63.6)	52 (72.3)	

PFS: T790M positive versus T790M negative



Other Mutations: PFS in patients receiving BIBW 2992



Diagnostic assessment in
plasma?

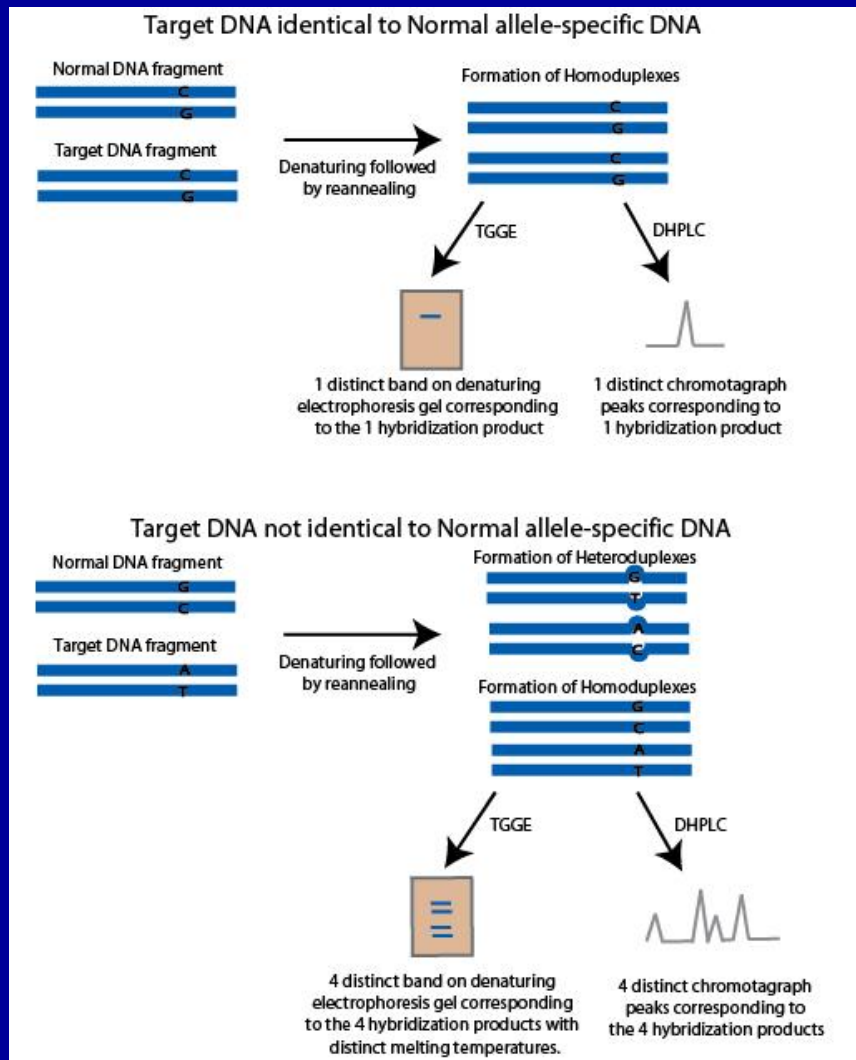
Finding EGFR Mutation in Plasma DNA by PCR: Spanish Study

	Value	Response (all patients)‡	n (%)
Erlotinib therapy, n (%)			
First-line	113 (52.1)	CR	24 (12.2)
Second- or third-line	104 (47.9)	PR	115 (58.4)
		CR / PR	139 (70.6)
EGFR mutation, n (%)			
del 19	135 (62.2)	SD	38 (19.3)
L858R	82 (37.8)	PD	20 (10.2)
		SD / PD	58 (29.4)
EGFR mutation in serum, n (%)*			
del 19	64 (39.0)	‡Evaluated in 197 patients	
L858R	33 (20.1)		
Not detected	67 (40.9)		

False Negative Rate

*Evaluated in the serum of 164 patients

Finding EGFR mutation in plasma by Denaturing High-Performance Liquid Chromatography (DHPLC): A Beijing Study



- 230 pts with tumor samples for EGFR mutation analysis
- DHPLC performed in plasma
- 102 pts received gefitinib (second line)

Diagnostic Utility of Plasma DNA (EGFR mutation)

Plasma	Tumor		Total
	EGFR mut Positive	EGFR mut Negative	
EGFR mut Positive	63	16 ← False Positive Rate=20.2%	79
EGFR mut Negative	14 ← False negative Rate=18.8%	137	151
Total	77	153	(230)

IPASS: Japanese Population

Patients recruited in Japan (n=233)

cfDNA extracted from
pre-dose serum samples

and/or

DNA extracted from
paraffin-embedded
archival tumor tissue

EGFR mutations detected by ARMS

cfDNA

EGFR M+: $\geq 1/21$ mutations^a (n=46)
EGFR M-: 0/21 mutations (n=148)
EGFR M unknown^c: (n=39)

Tumor tissue

EGFR M+: $\geq 1/29$ mutations^b (n=56)
EGFR M-: 0/29 mutations (n=35)
EGFR M unknown^c: (n=142)

Comparison of cfDNA vs tumor tissue EGFR mutations based on 21
mutations analyzed for cfDNA

Comparison of EGFR mutation status in cfDNA and tumor samples

Patients with known cfDNA and tumor EGFR mutation status (n=86)

cfDNA, n	Tumor tissue, n		Total
	EGFR M+	EGFR M-	
EGFR M+	22	0	22
EGFR M-	29	35	64
Total	51	35	86

- No false positive results
- Specificity and positive predictive value 100%
- 29/51 (56.9%) of tumor EGFR M+ were cfDNA EGFR M- (false negatives)
- Sensitivity 43.1% (22/51), negative predictive value 54.7% (35/64)
- 57/86 (66.3%) concordance

ARMS vs DHPLC

	Sensitivity	Specificity	Positive predictive value
IPASS Japanese subgroup (by ARMS)	43.1%	100%	100%
Bai and Wang (by DHPLC)	81.8%	89.5%	79.7%

Digital PCR

Single-Molecule Detection of Epidermal Growth Factor Receptor Mutations in Plasma by Microfluidics Digital PCR in Non – Small Cell Lung Cancer Patients

Tony K.F. Yung,^{1,2} K.C. Allen Chan,^{1,2} Tony S.K. Mok,^{1,3} Joanna Tong,⁴ Ka-Fai To,⁴ and Y.M. Dennis Lo^{1,2,5}

Clin Cancer Res 2009;15(6) March 15, 2009

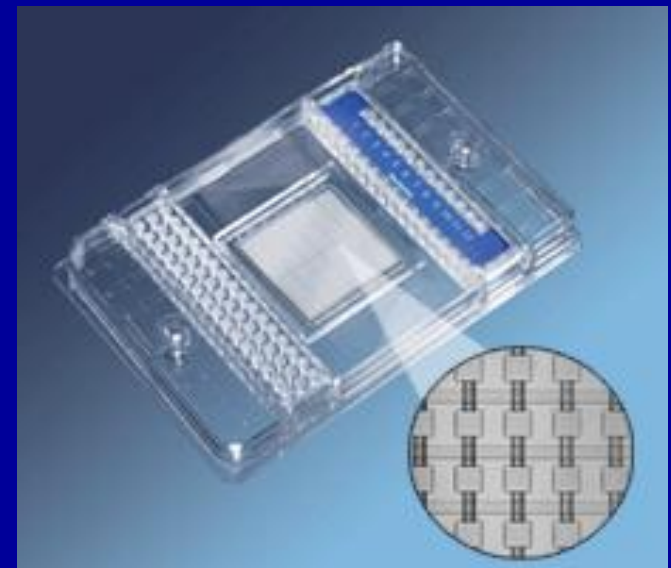
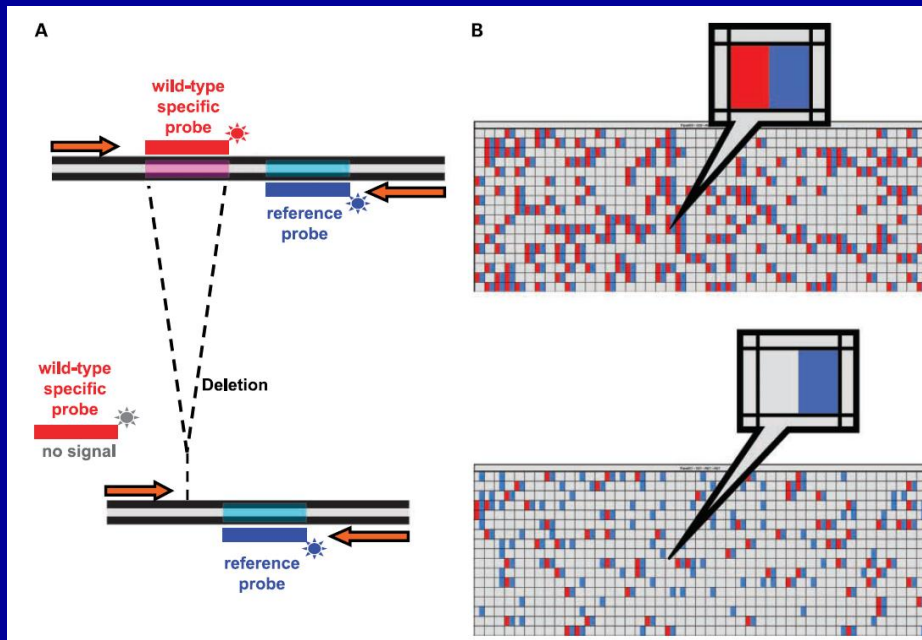


Table 2. Digital PCR detection of *EGFR* mutations in plasma collected before treatment

Patient	Tumor tissue		Plasma		Response to TKI treatment if treated with TKI*	
	CSGE and sequencing analysis ^{† ‡}	Digital PCR analysis [§]		Digital PCR analysis [§]		
		Del19 mutant percentage	L858R mutant percentage	Mutation		Concentration (copies/mL)
(A) Mutations detected by digital PCR and by CSGE and sequencing						
Case 8	L858R	ND	40	L858R	3.2	PR
Case 15	L858R	ND	19	L858R	55	PD
Case 20	L858R	ND	23	L858R	3.2	—
Case 29	L858R	ND	87	L858R	29	—
Case 38	L858R	ND	39	L858R	34,000	CR
Case 39	L858R	ND	26	L858R	9.7	PR
Case 37	L858R	ND	5.2	None	ND	—
Case 11	Del19	65	ND	Del19	21	PR
Case 13	Del19	42	ND	Del19	140	—
Case 17	Del19	38	ND	Del19	890	—
Case 31	Del19	68	ND	Del19	200	—
Case 40	Del19	32	ND	Del19	49	—
(B) Mutations detected by digital PCR (CSGE and sequencing was unsuccessful)						
Case 18	Failed	56	3.9	Del19	22	—
Case 26	Failed	—	—	—	00	PR
Case 30	Failed	—	—	—	52	—
Case 34	Failed	—	—	—	00	—
(B) Mutations detected by digital PCR (CSGE and sequencing was successful)						
Case 3	Wild-type only	—	—	—	ND	—
Case 4	Wild-type only	—	—	—	ND	—
Case 19	Wild-type only	—	—	—	ND	—
(C) No mutation detected in tumor tissue						
Case 5	Wild-type only	—	—	—	ND	—
Case 6	Wild-type only	ND	ND	None	ND	—
Case 10	Wild-type only	ND	ND	None	ND	—
Case 14	Wild-type only	ND	ND	None	ND	—
Case 16	Wild-type only	ND	ND	None	ND	—
Case 21	Wild-type only	ND	ND	None	ND	—
Case 22	Wild-type only	ND	ND	None	ND	—
Case 23	Wild-type only	ND	ND	None	ND	—
Case 24	Wild-type only	ND	ND	None	ND	—
Case 25	Wild-type only	ND	ND	None	ND	—
Case 27	Wild-type only	ND	ND	None	ND	—
Case 28	Wild-type only	ND	ND	None	ND	—
Case 32	Wild-type only	ND	ND	None	ND	—
Case 33	Failed	ND	ND	None	ND	—
Case 35	Failed	ND	ND	None	ND	—
Case 36	Wild-type only	ND	ND	None	ND	—

Sensitivity: 92%
Specificity: 100%

Drug selection

Gefitinib versus Erlotinib

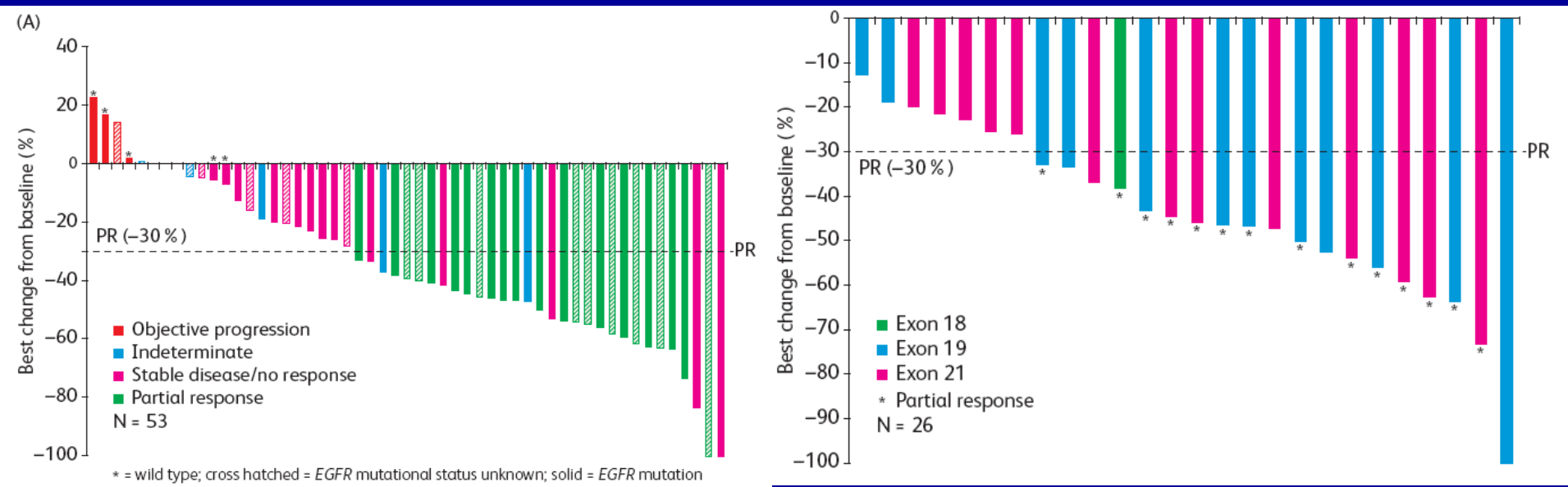


Treatment outcomes of first line EGFR TKI

Author	Study	N (EGFR mut +)	RR	Median PFS
Mok et al	IPASS	132	71.2%	9.8 months
Lee et al	First-SIGNAL	27	84.6%	8.4 months
Mitsudomi et al	WJTOG 3405	86	62.1%	9.2 months
Maemondo et al	NEJGSG002	114	73.7%	10.8 months
Rosell et al (1 st +2 nd line)	SLCG	197	70.5%	14.0 months
Zhou et al	OPTIMAL	NA	NA	NA
Rosell	EURTAC	NA	NA	NA

Mok et al NEJM 2009, Lee et al WCLC 2009, Mitsudomi et al Lancet Oncology 2010, Maemondo NEJM 2010
Rosell et al NEJM 2009

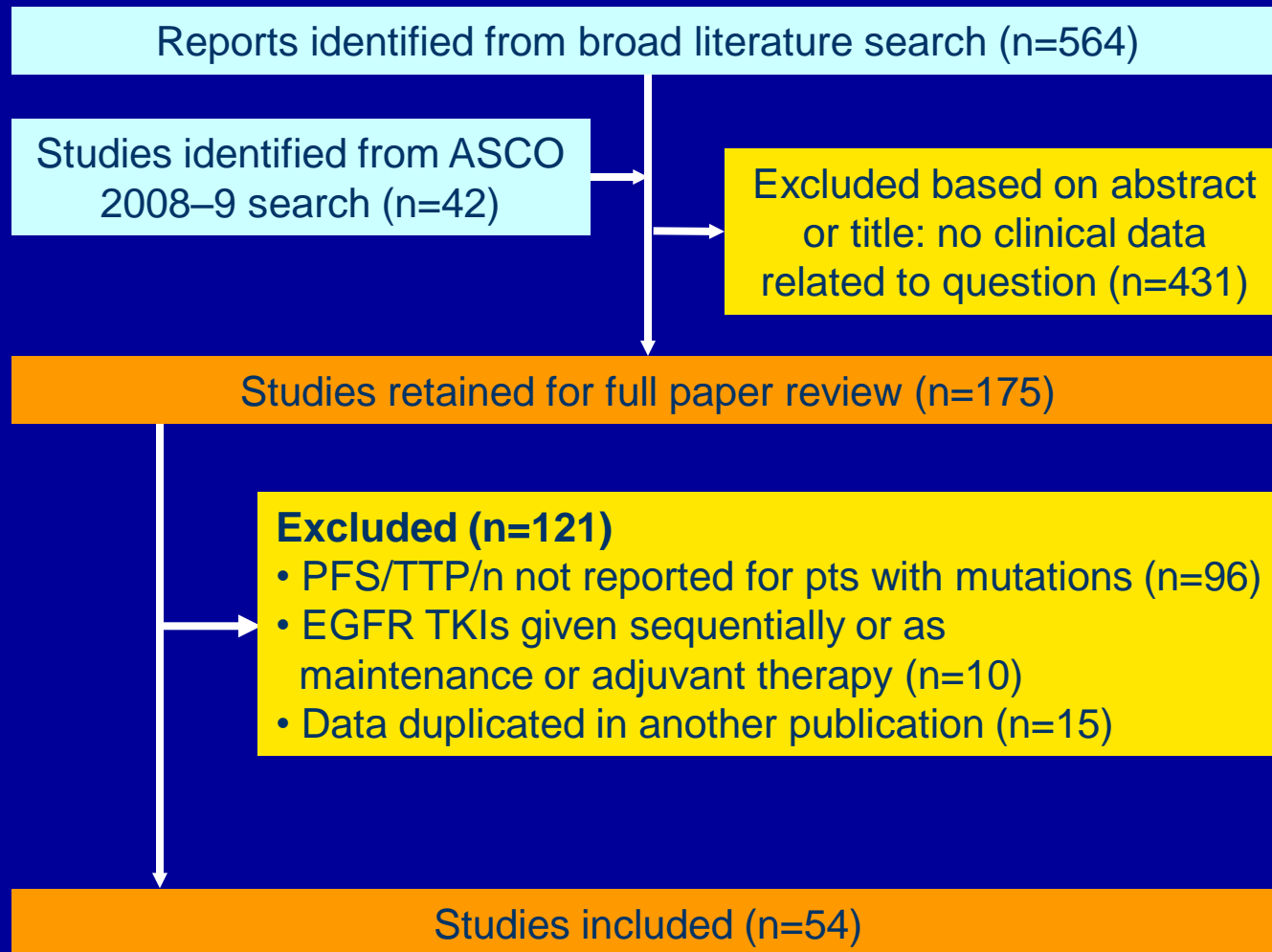
Irreversible EGFR TKI: PF299804



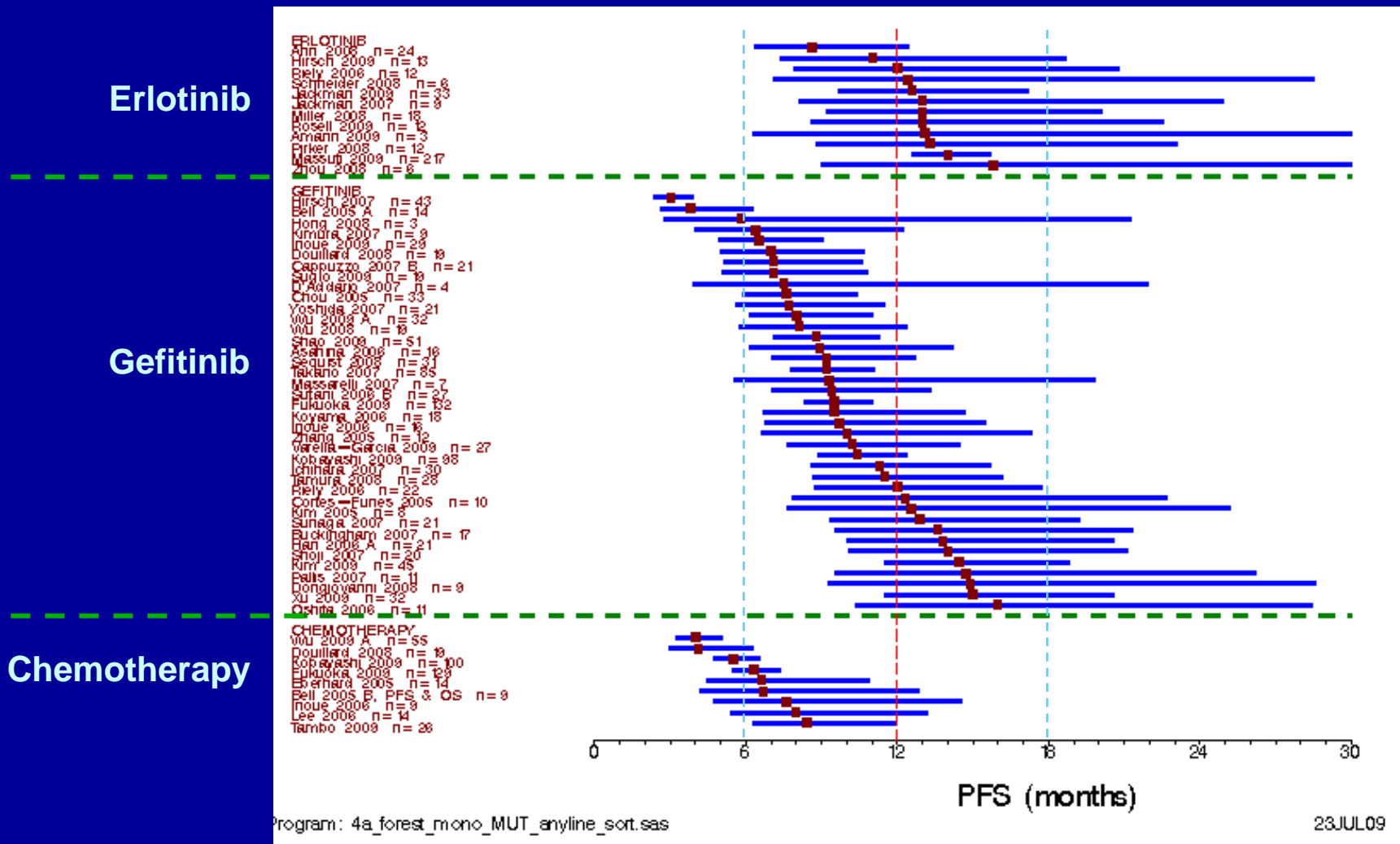
Non/light smoker, adenocarcinoma

EGFR Mutation

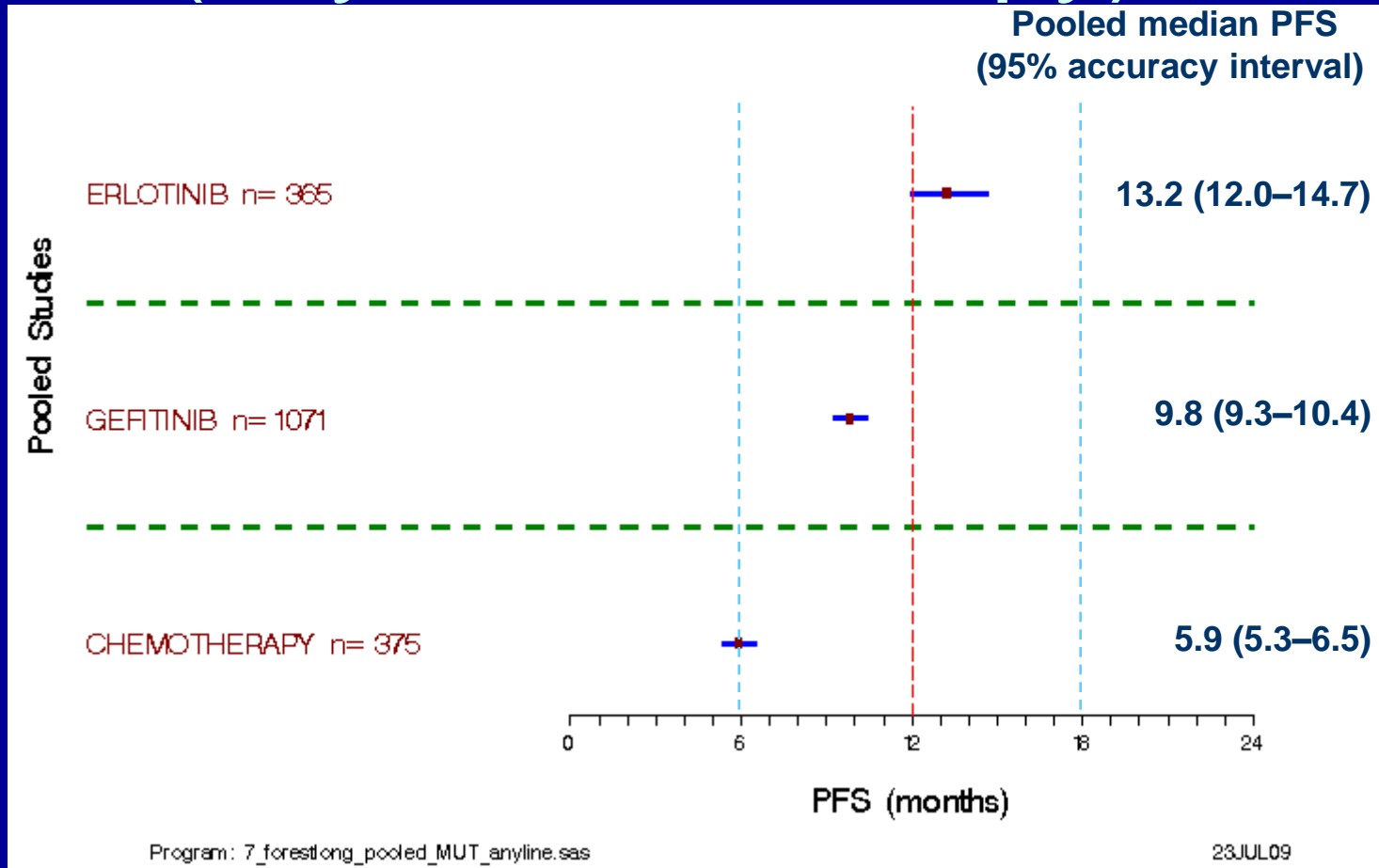
Pooled Analysis



Median PFS from individual studies 90% accuracy intervals (any line of therapy)



Pooled analysis (any line of therapy)



Permutation test for estimated pooled median PFS (1,000 iterations)
EGFR TKI vs chemotherapy p=0.000 (two-sided)

Toxicity

Adverse Event	Gefitinib (N = 607)	
	All Adverse Events	CTC Grade 3, 4, or 5
Rash or acne†	402 (66.2)	19 (3.1)
Diarrhea	283 (46.6)	23 (3.8)
Dry skin	145 (23.9)	0
Anorexia†	133 (21.9)	9 (1.5)
Pruritus†	118 (19.4)	4 (0.7)
Stomatitis†	103 (17.0)	1 (0.2)
Asthenic conditions†	102 (16.8)	2 (0.3)
Nausea	101 (16.6)	2 (0.3)
Paronychia	82 (13.5)	2 (0.3)
Vomiting	78 (12.9)	1 (0.2)
Constipation	73 (12.0)	0
Alopecia	67 (11.0)	0
Neurotoxic effects†	66 (10.9)	2 (0.3)
Myalgia	47 (7.7)	3 (0.5)
Arthralgia	39 (6.4)	1 (0.2)
Neutropenia‡		
Any	NA	22 (3.7)
Febrile	1 (0.2)	1 (0.2)
Anemia‡	NA	13 (2.2)
Leukopenia‡	NA	9 (1.5)

	All Toxicities N (%)	Grade 3-4 Toxicities N (%)
Skin	151 (69.6)	16 (7.4)
Diarrhea	95 (43.8)	8 (3.7)

↑
SLCG

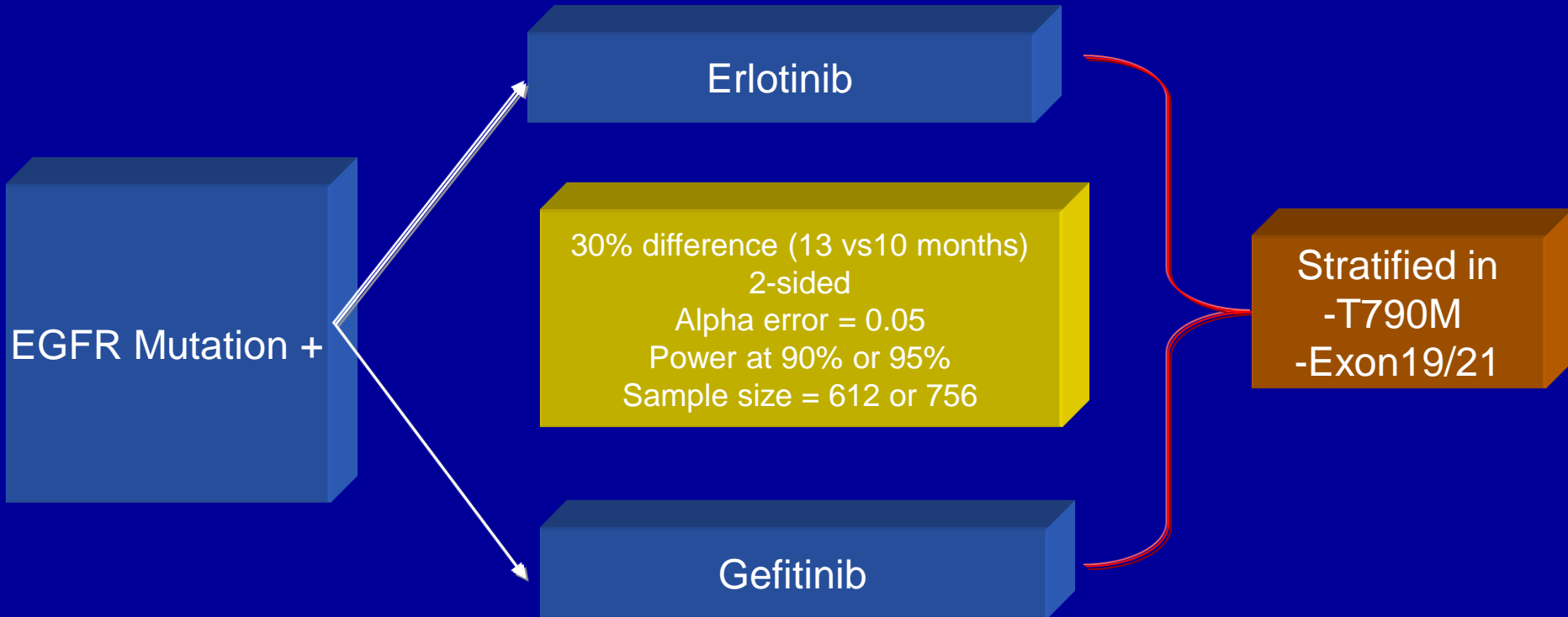
← IPASS

C-TONG 0901

Erlotinib versus gefitinib in advanced non small cell lung cancer with exon21 mutation
: A multi-center randomized phase II trial

Current Enrollment	Target Sample size	Current Sample Size	Date of First Pt	Date of Last Pt
Status	70	NA	2009-7-13	NA

Head to head comparison?



Summary

- Diagnostic assessment
 - Be aware of false negative result in EGFR mutation analysis (variability in sensitivity among different testing methods)
 - T790M is potentially predictive
 - Role of first line TKI in “other mutation” remains unclear
- Drug selection
 - Lack of direct comparative data

Blind leading the blind

