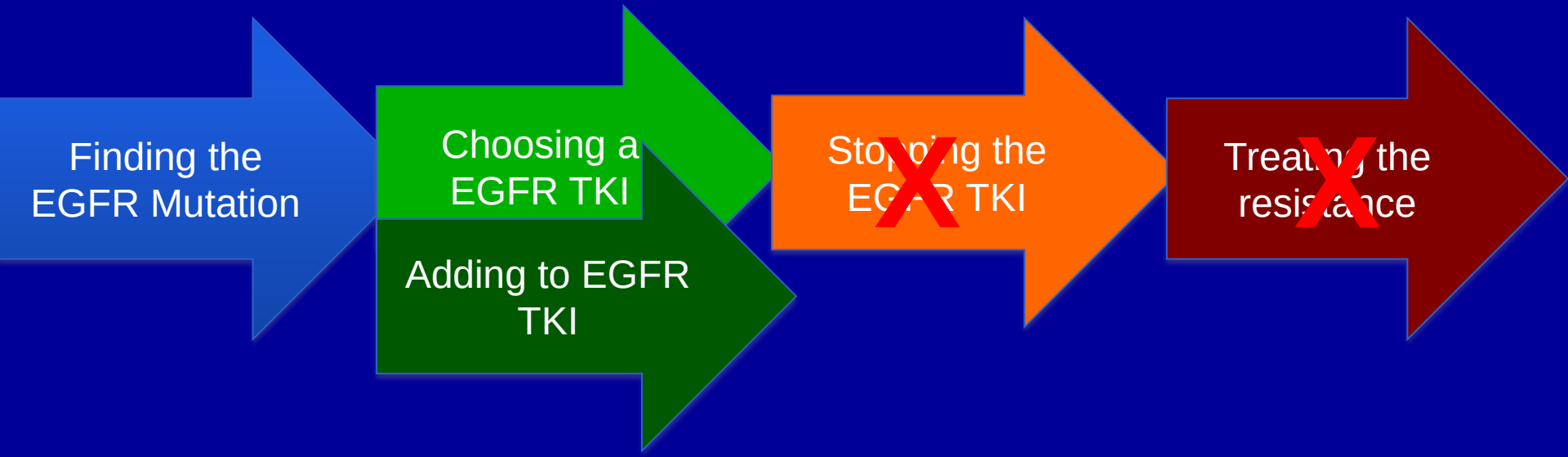
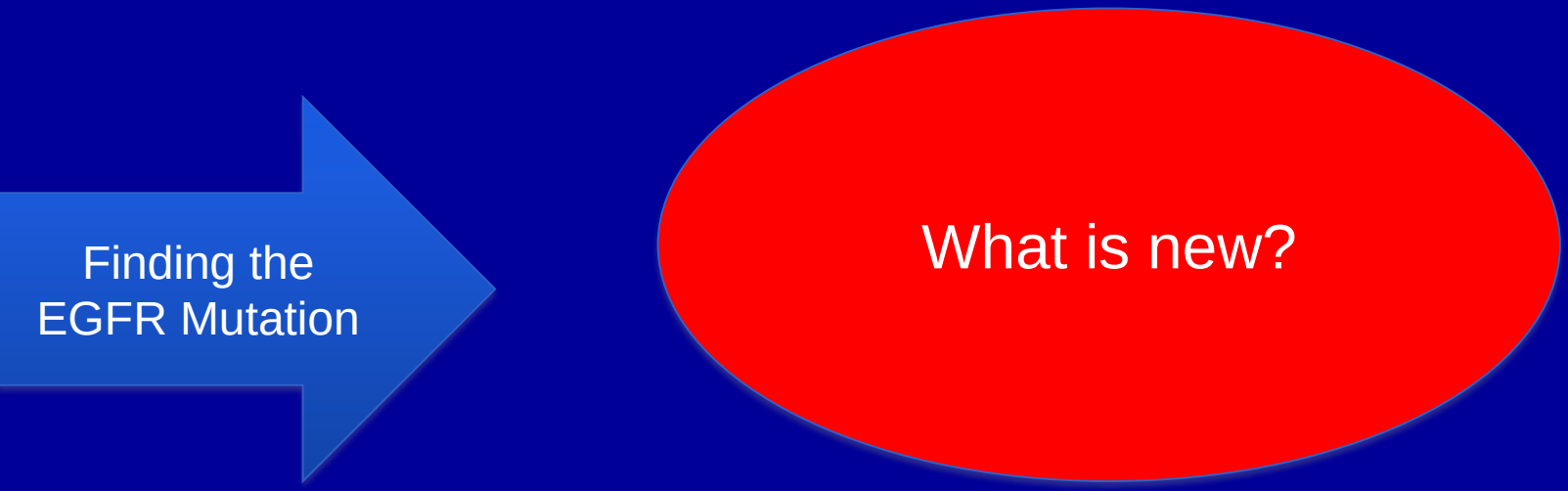
An EGFR Journey

Professor Tony Mok
Li Shu Fun Medical Foundation Professor of Clinical Oncology
The Chinese University of Hong Kong

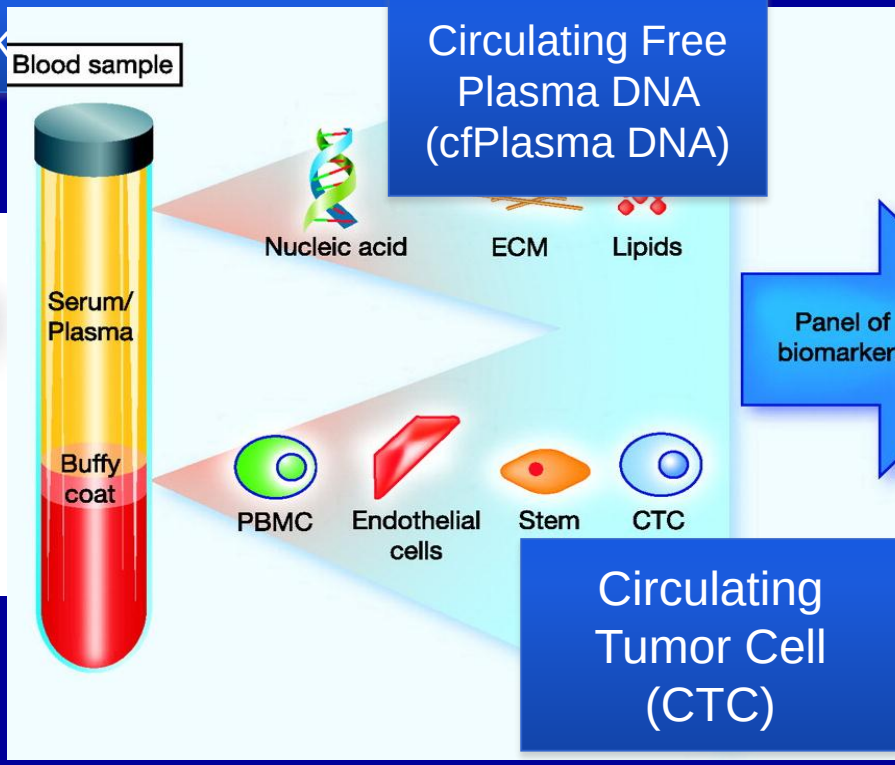
An EGFR Journey



An EGFR Journey



1wk 2wk



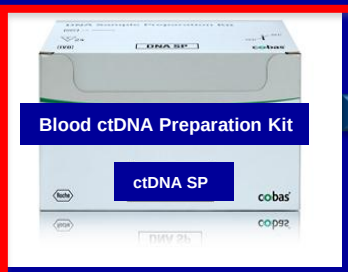
Circulating Free Plasma DNA (cfPlasma DNA)

Circulating Tumor Cell (CTC)

cobas® EGFR _ *blood* Test _ Kit Components

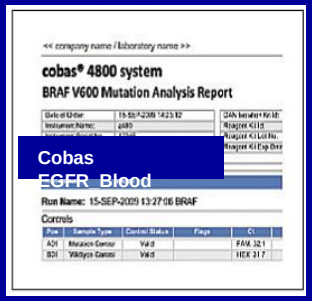
Utilizing most of the reagents in the cobas EGFR_FFPET test and requiring additional reagents and the blood-specific data analysis software

2 ml Plasma

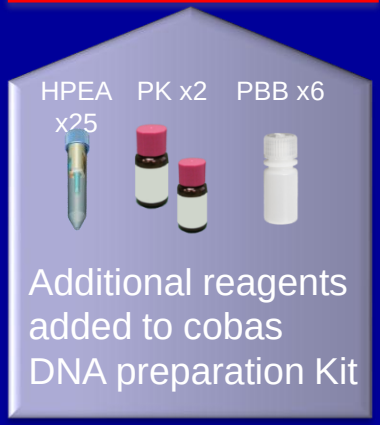


cobas **cell-free** DNA Preparation Kit (To be used for other blood based assays)

cobas EGFR _ *blood* Test
cobas 4800 v 2.0



cobas EGFR _ *Blood*



Additional reagents added to cobas DNA preparation Kit

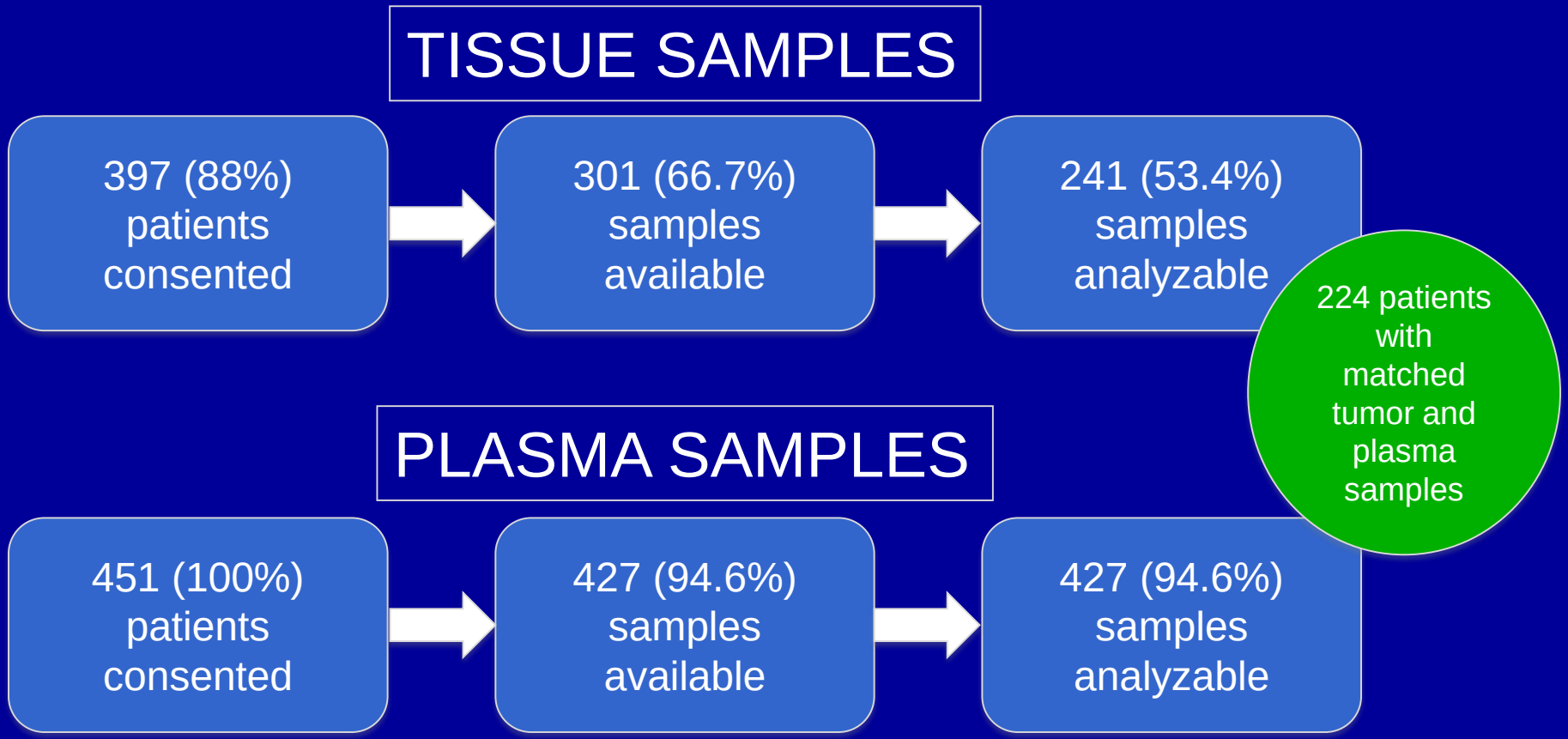
Tube	FAM	HEX	JA270
1	EX 19Del		S768I
2	L858R		T790M
3	G719X	L861Q*	EX 20Ins

*New primer and probe for L861Q

Blood-specific cutoffs; Blood-specific data analysis software

Mok et al ASCO 2013

FASTACT 2: Tumor versus plasma DNA for *EGFR* Mutation Analysis

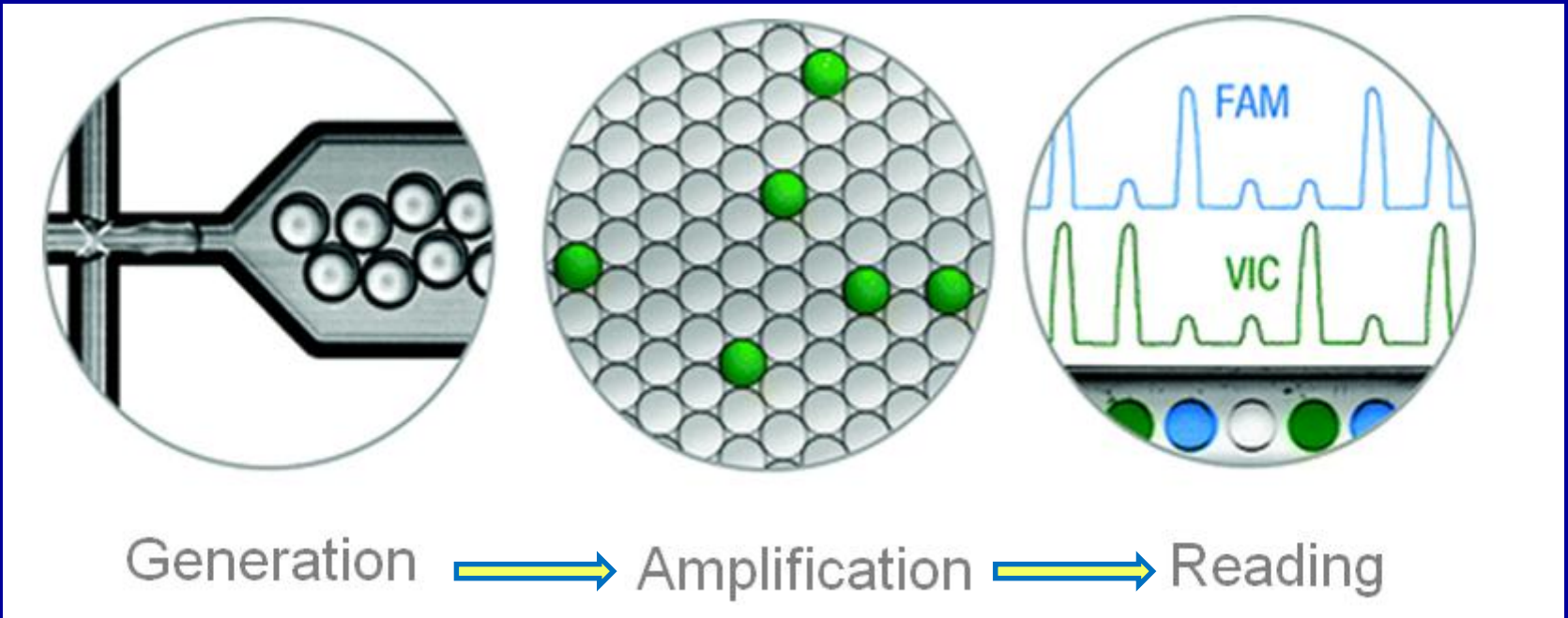


Concordance between tumor and plasma samples

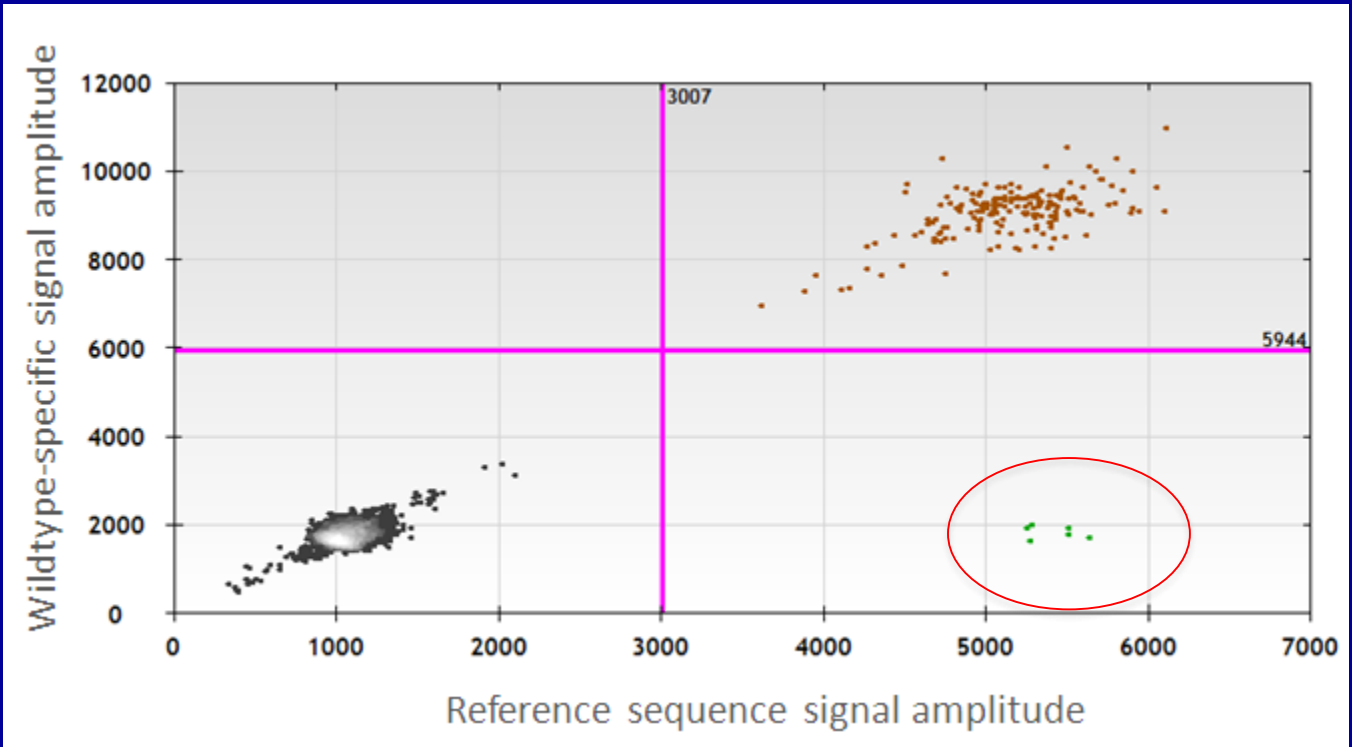
- Total of 224 patients had both tumor and baseline plasma samples with available *EGFR* mutation analysis results (Table 3)
  - Sensitivity: 77% (69/90)
  - Specificity: 96% (129/134)
  - Positive predictive value: 93% (69/74)
  - Negative predictive value: 86% (129/150)
  - Overall concordance: 88% (198/224)

***EGFR* Activating Mutations**	**p-EGFR Mut+ (Plasma)**	**p-EGFR Mut- (Plasma)**	**Total**
t-EGFR Mut+ (Tumor)	69	21	90
t-EGFR Mut- (Tumor)	5	129	134
Total	74	150	224

Droplet digital PCR (ddPCR)

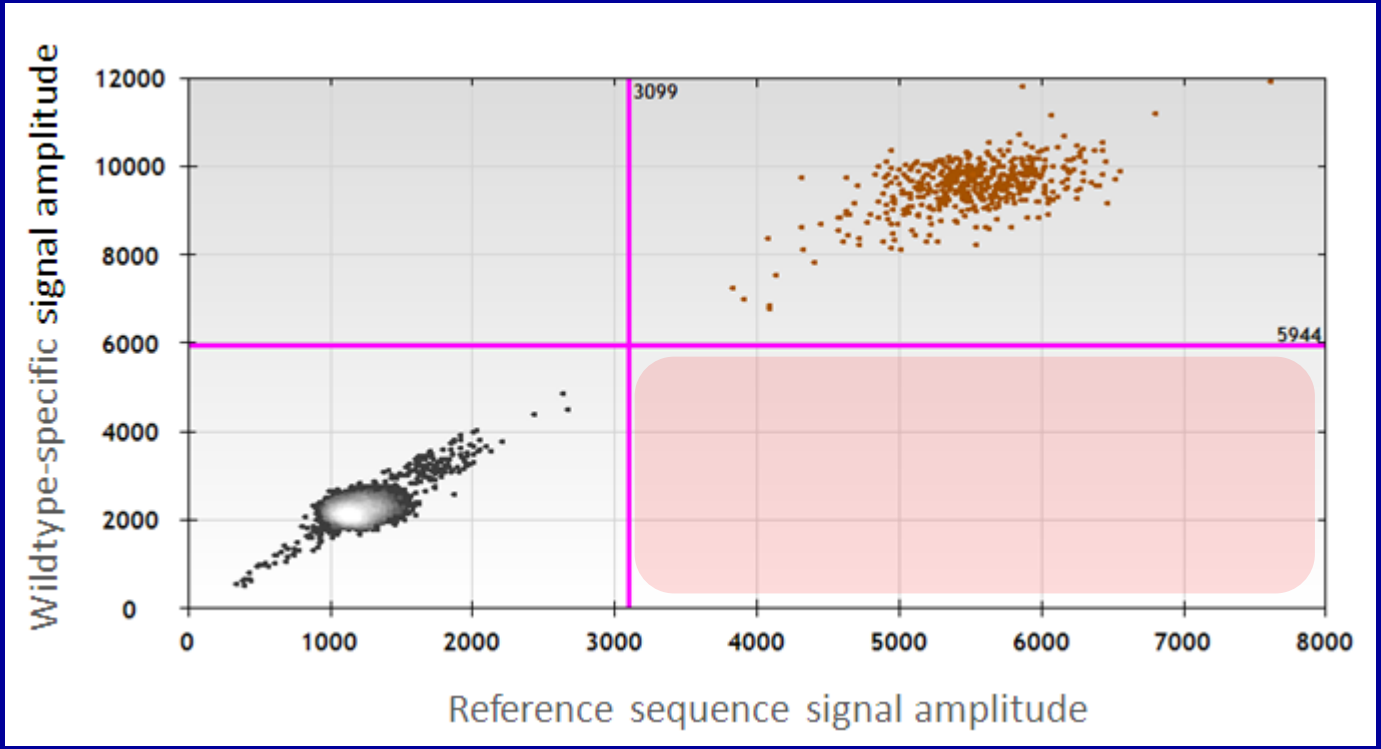


Positive result on exon 19 deletion assay



Plasma sample 214
Mutant concentration:72 copies/ml plasma
Fraction concentration : 3.2%

Negative result on exon 19 deletion assay



Analyzing plasma and tumor sample from ASPIRATION study and matched control (n=197)

- Tumor sample: COBAS *EGFR* Mutation Test

- Plasma sample: Droplet digital PCR

Lee et al WCLC 2013

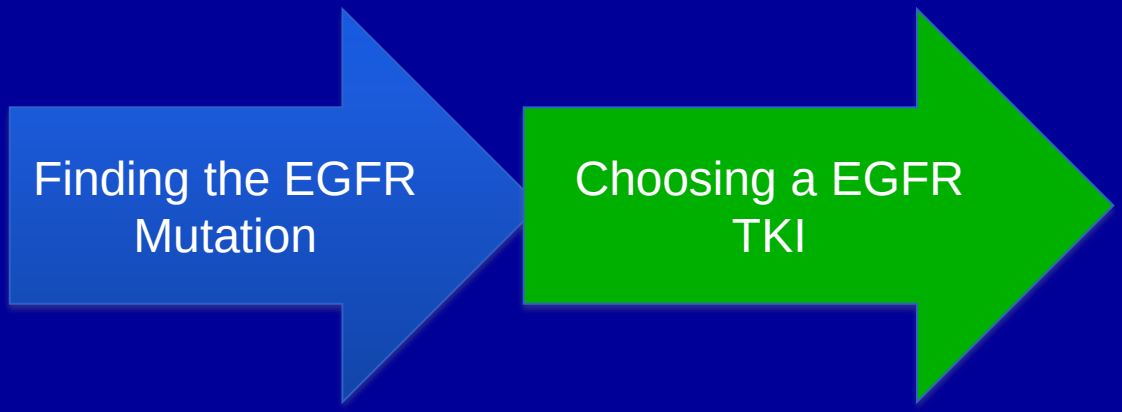
Diagnostic utility of digital PCR for detection of EGFR mutation

	POS in plasma	NEG in plasma	
POS in tumor	117	27	144
NEG in tumor	0	53	53
	117	80	197

Droplet digital PCR	
Sensitivity	81%
Specificity	100%
Positive Predictive Value	100%
Concordance	86%

Blood-based molecular analysis may optimize the timing and coverage

An EGFR Journey

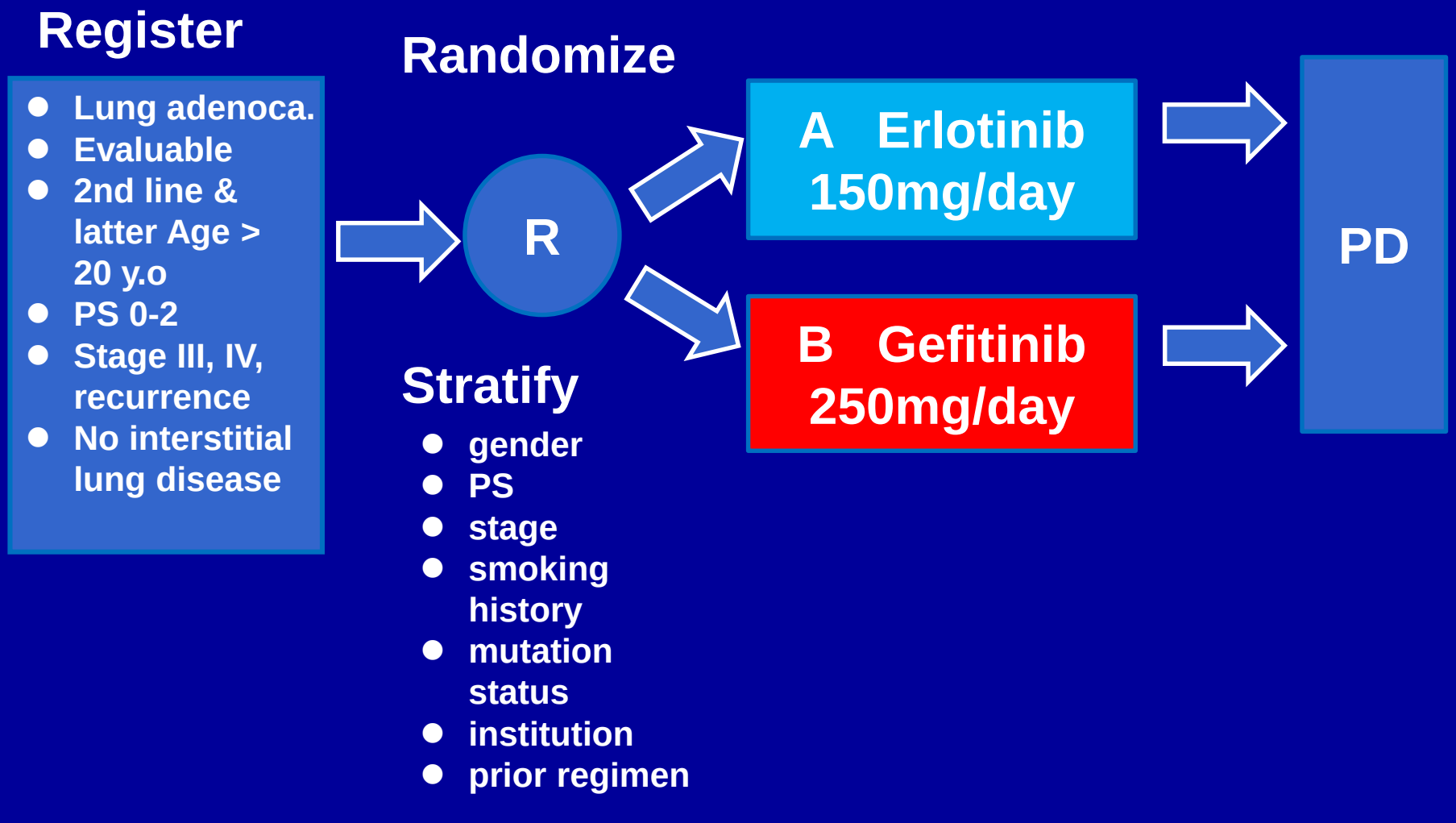


Where we are?

Author	Study	N (EGFR mut +)	RR	Median PFS
Mok et al	IPASS	132	71.2% vs 47.3	9.8 vs 6.4 months
Lee et al	First-SIGNAL	27	84.6% vs 37.5%	8.4 vs 6.7 months
Mitsudomi et al	WJTOG 3405	86	62.1% vs 32.2%	9.2 vs 6.3 months
Maemondo et al	NEJGSG002	114	73.7% vs 30.7%	10.8 vs 5.4 months
Zhou et al	OPTIMAL	154	83% vs 36%	13.1 vs 4.6 months
Rosell et al	EURTAC	135	56% vs 18%	9.2 vs 4.8 months
Yang et al	LUX Lung 3	345	56% vs 22%	11.1 vs 6.9 months
Wu et al	LUX Lung 6	364	67% vs 23%	11.0 vs 5.6 months

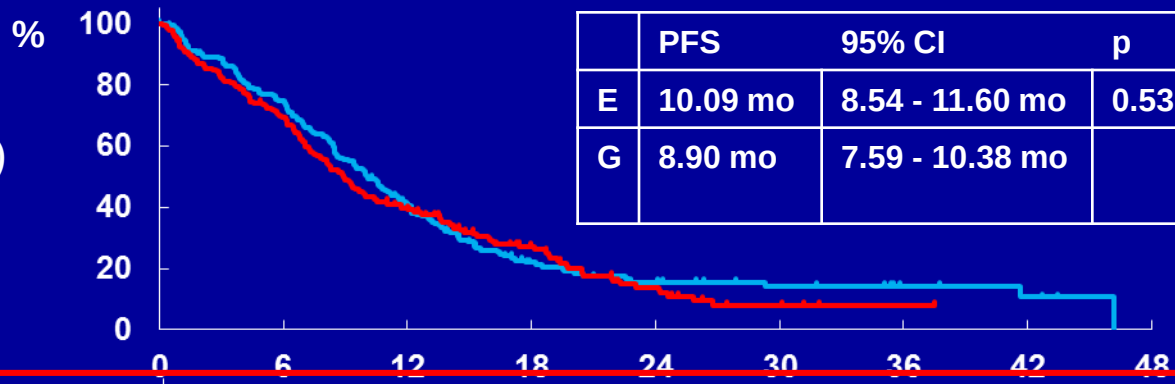
Mok et al NEJM 2009, Lee et al WCLC 2009, Mitsudomi et al Lancet Oncology 2010, Maemondo NEJM 2010 Zhou et al Lancet Oncol 2010; Yang et al JCO ePub; Wu et al Lancet Oncol: In Press

ASCO 2014: WJOG5108 Study



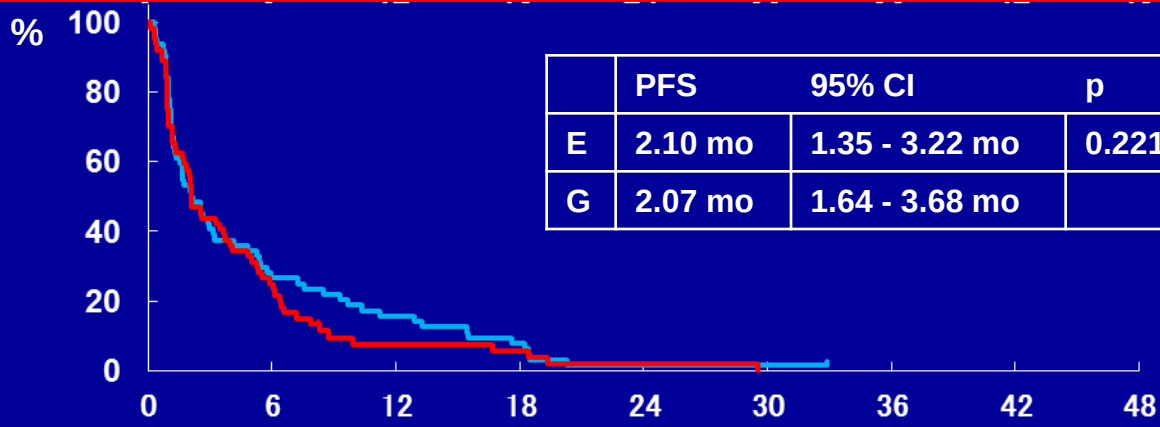
Katakami et al ASCO 2014

EGFR mutation (+)



	PFS	95% CI	p
E	10.09 mo	8.54 - 11.60 mo	0.532
G	8.90 mo	7.59 - 10.38 mo	

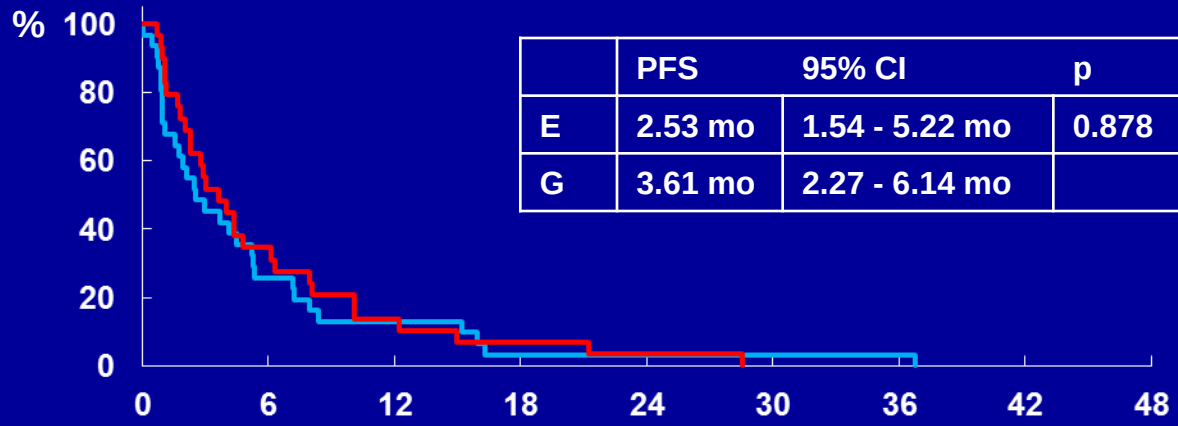
EGFR mutation (-)



	PFS	95% CI	p
E	2.10 mo	1.35 - 3.22 mo	0.221
G	2.07 mo	1.64 - 3.68 mo	

E
G

EGFR mutation
unknown

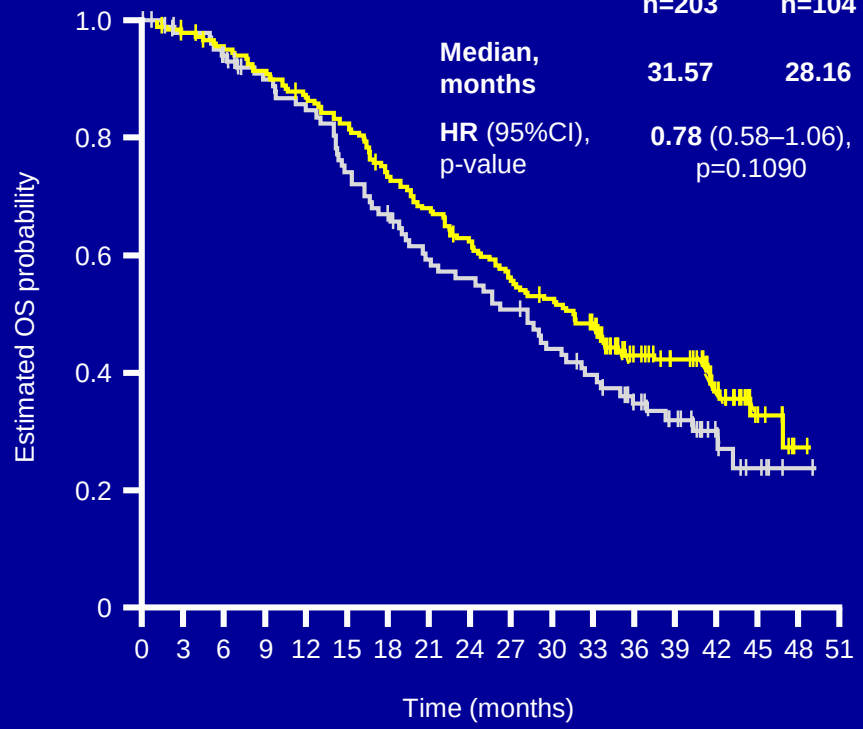


	PFS	95% CI	p
E	2.53 mo	1.54 - 5.22 mo	0.878
G	3.61 mo	2.27 - 6.14 mo	

From PFS to OS

LUX-Lung 3 and 6: OS in common mutations

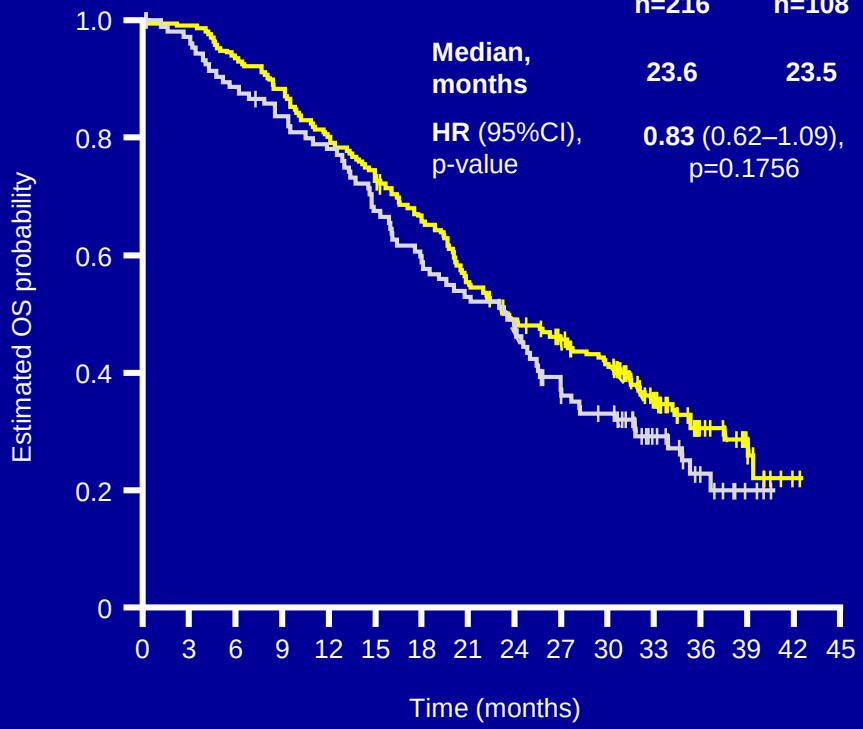
LUX-Lung 3



No of patients

Afatinib	203	197	188	181	171	162	143	133	121	108	101	90	58	49	32	9	1	0
Pem/Cis	104	98	92	86	81	71	63	55	52	47	40	35	26	20	10	5	1	0

LUX-Lung 6

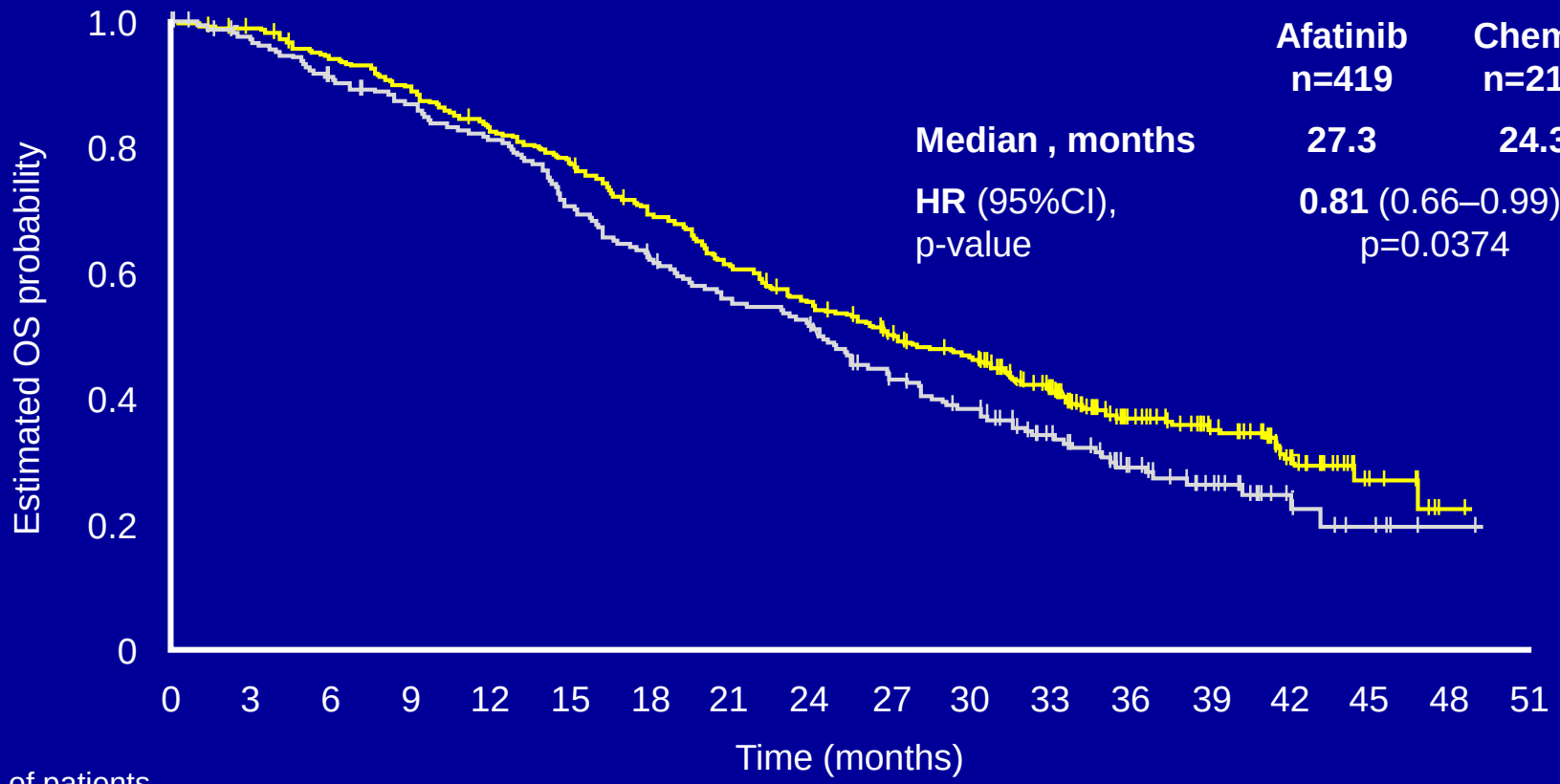


No of patients

Afatinib	216	214	202	190	172	158	141	118	104	93	80	51	19	9	1	0	
Gem/Cis	108	101	93	87	81	70	61	55	49	36	30	17	8	3	0	0	

Presented by: James Chih-Hsin Yang

Combined OS analysis: common mutations (n=631)



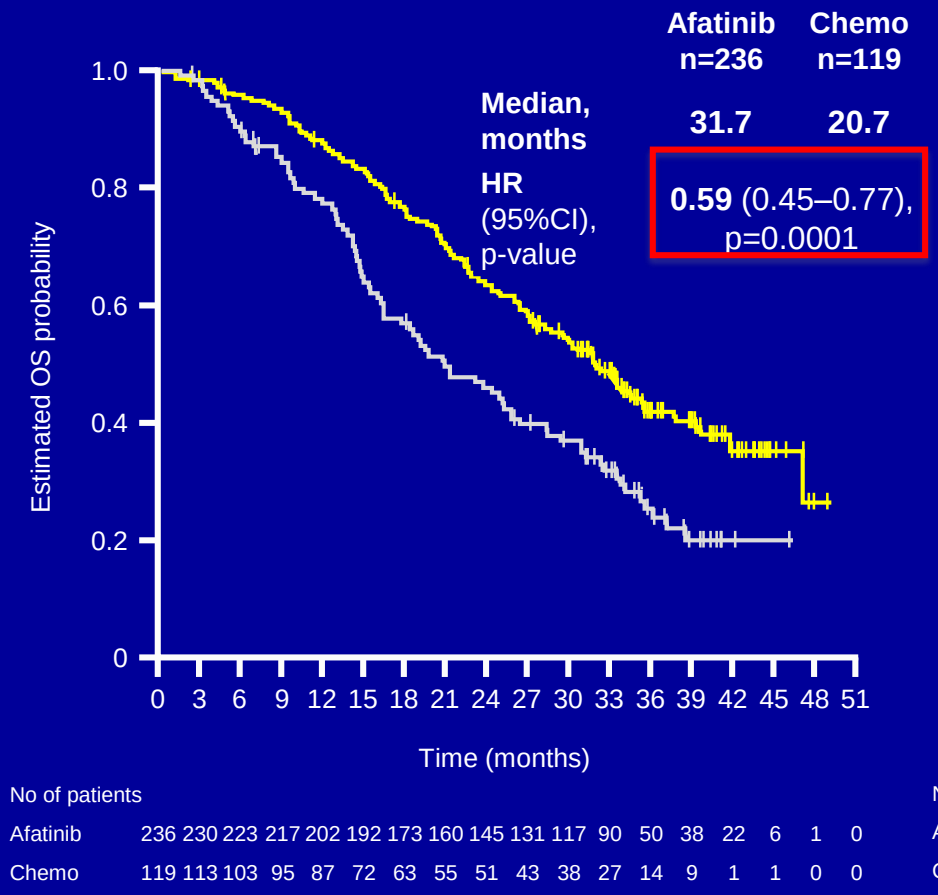
	Afatinib n=419	Chemo n=212
Median , months	**27.3**	**24.3**
HR (95%CI), p-value	**0.81** (0.66–0.99), p=0.0374	

No of patients

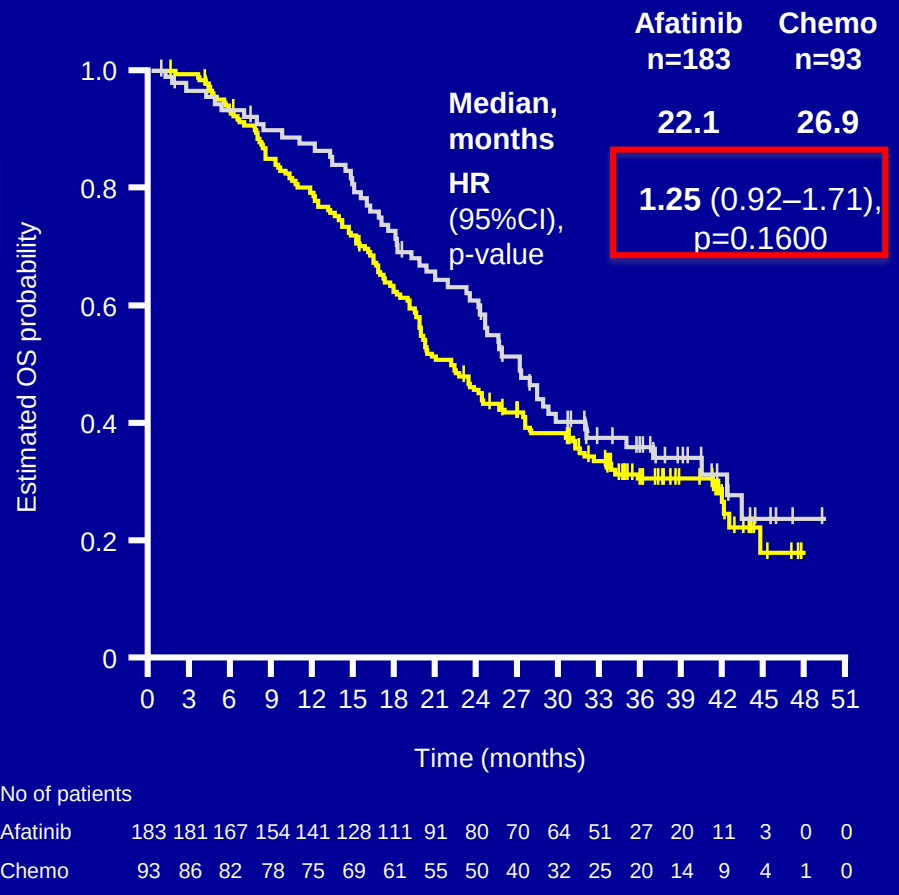
Afatinib	419	411	390	371	343	320	284	251	225	201	181	141	77	58	33	9	1	0
Chemo	212	199	185	173	162	141	124	110	101	83	70	52	34	23	10	5	1	0

Presented by: James Chih-Hsin Yang

Two subgroups of LUX Lung 3 and 6 OS analysis



Exon 19



Exon 21

Direct comparison: LUX Lung 7 Randomized IIb Study

- Is Afatinib better than Gefitinib in patients with EGFR mutation?

ARCHER 1050: Randomized Phase III Study Dacomitinib vs Gefitinib

Which patient you will send for EGFR mutation analysis?

What methods was used for EGFR mutation analysis?

How do you choose an EGFR TKI?

Do you treat exon 19 and 21 differently?

Why do we observe an OS benefit in exon 19 but not 21?

Other questions?