A Teaching Affiliate
of Harvard Medical School

Optimal Approach to EGFR-Mutant NSCLC

- *effect of EGFR variant on TKI selection* -

Alice T. Shaw, MD, PhD

February 11, 2017

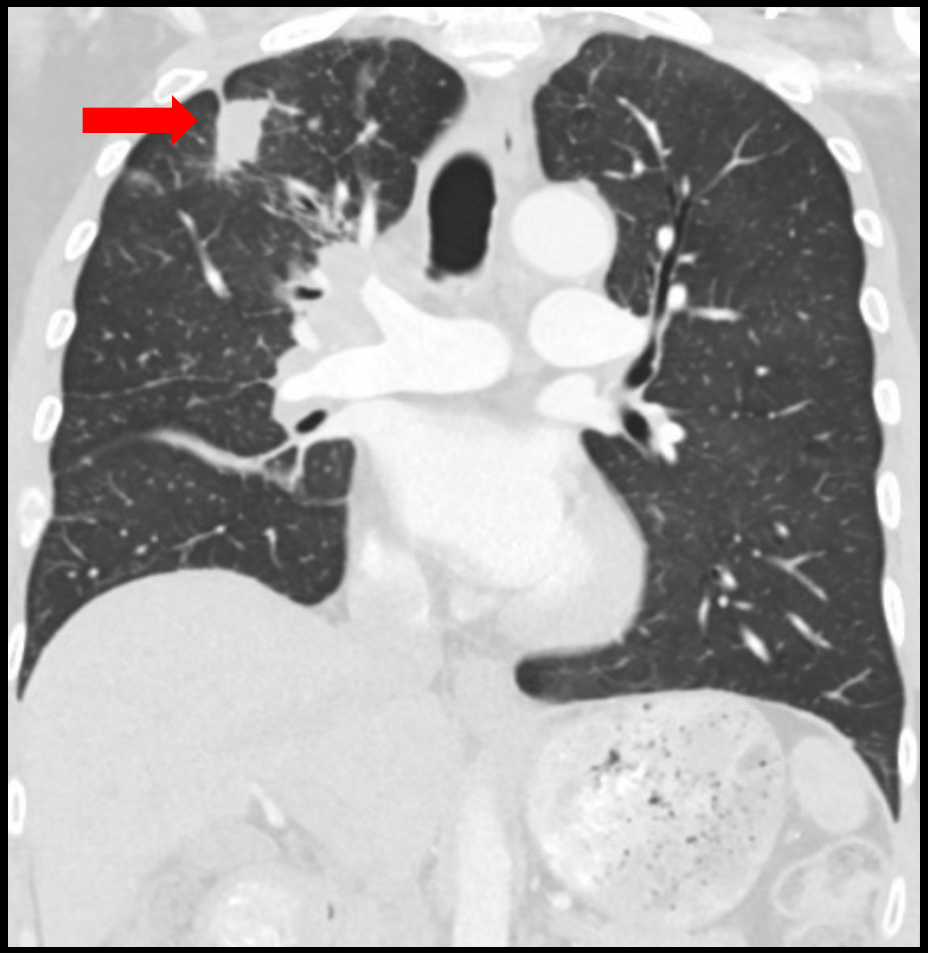
MASSACHUSETTS
GENERAL HOSPITAL

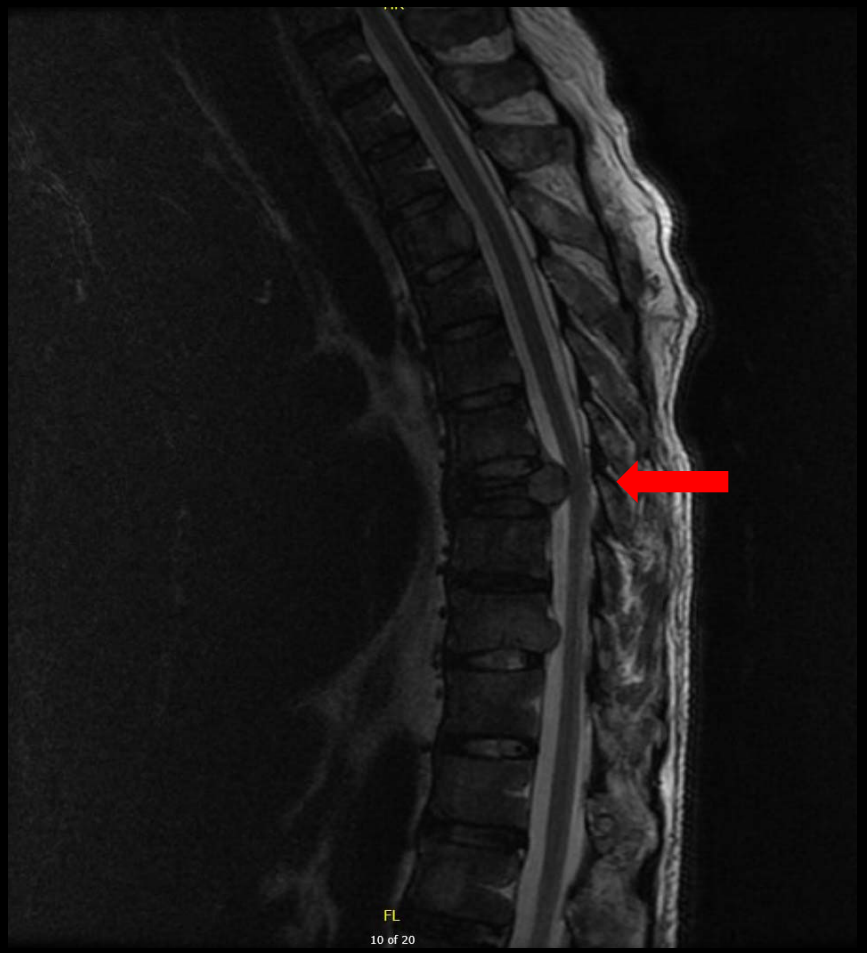
CANCER CENTER

Case

- 58 yo M Chinese neversmoker with only past medical history of nephrolithiasis
- One month prior to presentation, he developed mid back pain radiating around to the abdomen
- He was evaluated in Shanghai, where he lives part time. Initial workup was negative.
- PET-CT demonstrated FDG avid RUL nodule, R hilar and R mediastinal nodes, numerous FDG avid skeletal metastases, and compression fractures at T8 and L4
- He flew back to Boston and presented to the MGH ED

Case





Case

- He was started on steroids and pain meds
- Brain MRI with an asymptomatic 4 mm metastasis
- He was taken urgently to neurosurgical decompression, stabilization, and augmentation
- Specimen from the OR was submitted for rapid molecular testing, which demonstrated an EGFR ex19 deletion
- He had mild DIC but otherwise an uncomplicated post-op course
- He underwent post-op RT
- He was initiated on first-line afatinib

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Disclosures

Advisory Committee	EMD Serono Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc
Consulting Agreements	Blueprint Medicines, Daiichi Sankyo Inc, EMD Serono Inc, Ignyta Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Taiho Oncology Inc

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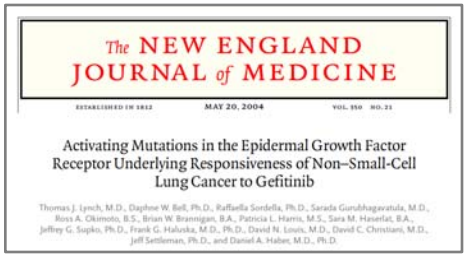
EGFR-mutant NSCLC: 2004-2016


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

***EGFR* mutations described as oncogenic drivers of NSCLC[1]**

T790M Resistance Mutation described[2]

ERLOTINIB and AFATINIB-
FDA approval for 1st-line EGFRm+ NSCLC

GEFITINIB-
FDA approval for 1st-line EGFRm+ NSCLC

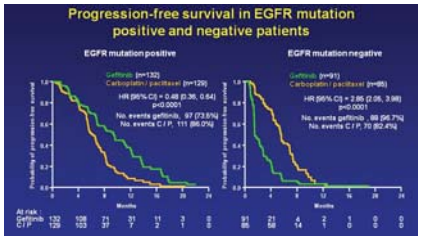
Plasma-based cobas v2
FDA approved as companion diagnostic for **erlotinib (activating EGFR mutations)**

2003 2004 2005 2009 2013 2014 2015 2016

GEFITINIB-
accelerated FDA approval for NSCLC after failure of docetaxel (later lost full approval for this indication)

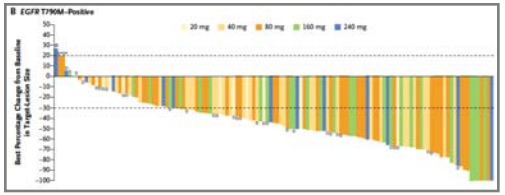
ERLOTINIB FDA approved for NSCLC after failure of ≥ 1 prior therapy

iPASS[3]



Ph1 studies of T790M-specific 3rd gen EGR TKIs start (osimertinib, rociletinib)

OSIMERTINIB-
FDA approval for second-line, T790M+ EGFRm+ NSCLC[4]



Plasma-based cobas v2
FDA approved as companion diagnostic for **osimertinib (T790M)**

1. Lynch, et al. NEJM 2004; 2. Pao, et al. PLoS Medicine 2005; 3. Mok, et al. NEJM 2005; 4. Janne, et al. NEJM 2015.

Study	N	Arms	Response Rate (%)	Med PFS (mo)	HR
IPASS	261	Gefitinib	71%	9.6	0.48 (.36, .64)
NEJM '09		Carbo/ paclitaxel	47%	6.3	
WJTOG 3405	228	Gefitinib	62%	9.2	0.49 (.35, .71)
Lan Onc '10		Cis/docetaxel	31%	6.3	
NEJ002	114	Gefitinib	74%	10.8	0.30 (.22, .50)
NEJM '09		Carbo/ paclitaxel	32%	5.5	
OPTIMAL	165	Erlotinib	83%	13.1	0.16 (.10, .26)
Lan Onc '11		Carbo/gem	36%	4.6	
EURTAC	174	Erlotinib	58%	9.7	0.37 (.25, .54)
Lan Onc' 12		Cis or carbo + doce or gem	15%	5.2	
LUX-Lung 3	345	Afatinib	69%	11.1 (*13.6*)	0.58 (.43,.78)
JCO '13		Cis/pem	44%	6.9 (*6.9*)	0.47 (.34,.65)

Despite significant advances, the median PFS for all three EGFR TKIs (erlotinib, gefitinib, afatinib) used in the first line setting remains between **9-13 months.**

LUX-Lung 3 and 6: design

- Stage IIIB/IV adenocarcinoma of the lung
- Presence of *EGFR* mutation in the tumor tissue*
- No prior treatment with chemotherapy for advanced/metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

2:1

Stratification by EGFR mutation type: Del19/L858R/other
and by race (LUX-Lung 3 only): Asian/non-Asian

Afatinib
40 mg orally once daily

LUX-Lung 3[1]:
Cisplatin + pemetrexed
up to 6 cycles

LUX-Lung 6[2]:
Cisplatin + gemcitabine
up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary end points: ORR, DCR, OS, PRO, safety

*EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A and G719C (or G719X), S768I.

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213.

LUX-Lung 3 and 6: populations

		LUX-Lung 3		LUX-Lung 6	
		Afatinib n=230	Pem/Cis n=115	Afatinib n=242	Gem/Cis n=122
Gender	Male	83 (36)	38 (33)	87 (36)	39 (32)
	Female	147 (64)	77 (67)	155 (64)	83 (68)
Age	median (range)	62 (28–86)	61 (31–83)	58 (29–79)	58 (27–76)
Race	Non-Asian	64 (28)	32 (28)	–	–
	Asian	166 (72)	83 (72)	242 (100)	122 (100)
Stage of disease	IIIB (wet)	20 (9)	17 (15)	16 (7)	6 (5)
	IV	210 (91)	98 (85)	226 (93)	116 (95)
ECOG status	0	92 (40)	41 (36)	48 (20)	41 (34)
	1	138 (60)	74 (64)*	194 (80)	81 (66)
EGFR mutation categories†	Common mutations	203 (88)	104 (90)	216 (89)	108 (89)
	Del19	112 (49)	57 (50)	124 (51)	62 (51)
	L858R	91 (40)	47 (41)	92 (38)	46 (38)
	Uncommon mutations	27 (12)	11 (10)	26 (11)	14 (11)

*Includes one patient with ECOG 2.
†May not total 100% due to rounding.

LUX-Lung 3 and 6: reported results

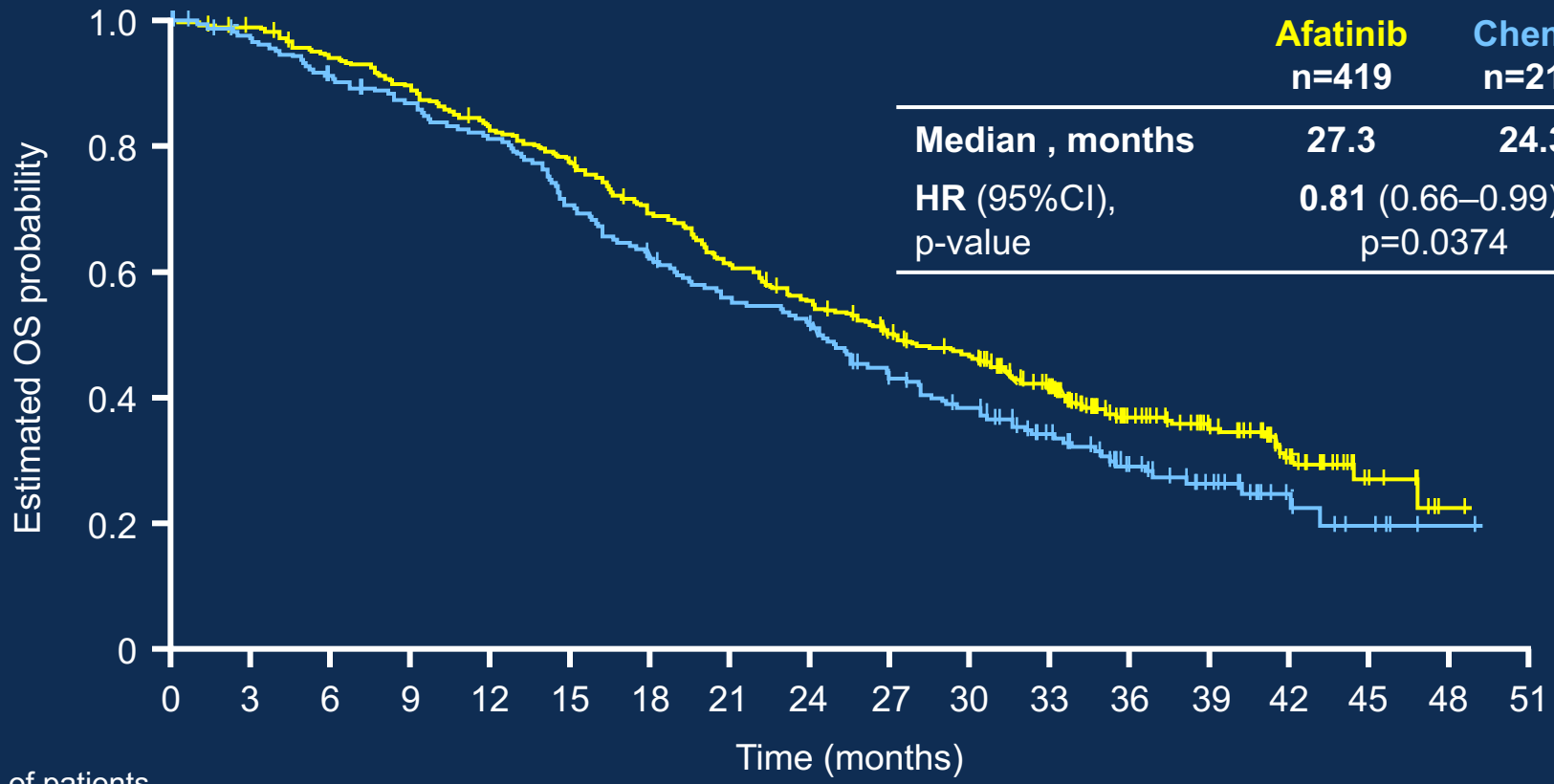
- Significant improvement over chemotherapy in PFS (primary endpoint)[1,2]

	Common mutations (Del19/L858R)			
	LUX-Lung 3 (n=307)		**LUX-Lung 6** (n=324)	
	Afatinib	Pem/Cis	Afatinib	Gem/Cis
Median PFS, mo	13.6	6.9	11.0	5.6
HR, p-value	**HR=0.47,** p<0.0001		**HR=0.25,** p<0.0001	

- Activity in some types of uncommon mutations (L861Q, G719X, S768I)[3]
- Improved symptom control and delay in worsening of cancer-related cough and dyspnea[4]

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213; 3. Yang et al. *J Thorac Oncol*. 2013;8:suppl 2 (O03.05); 4. Sequist et al. *J Thorac Oncol*. 2013;8:suppl 2 (P3.11-023).

Combined OS analysis: common mutations (n=631)

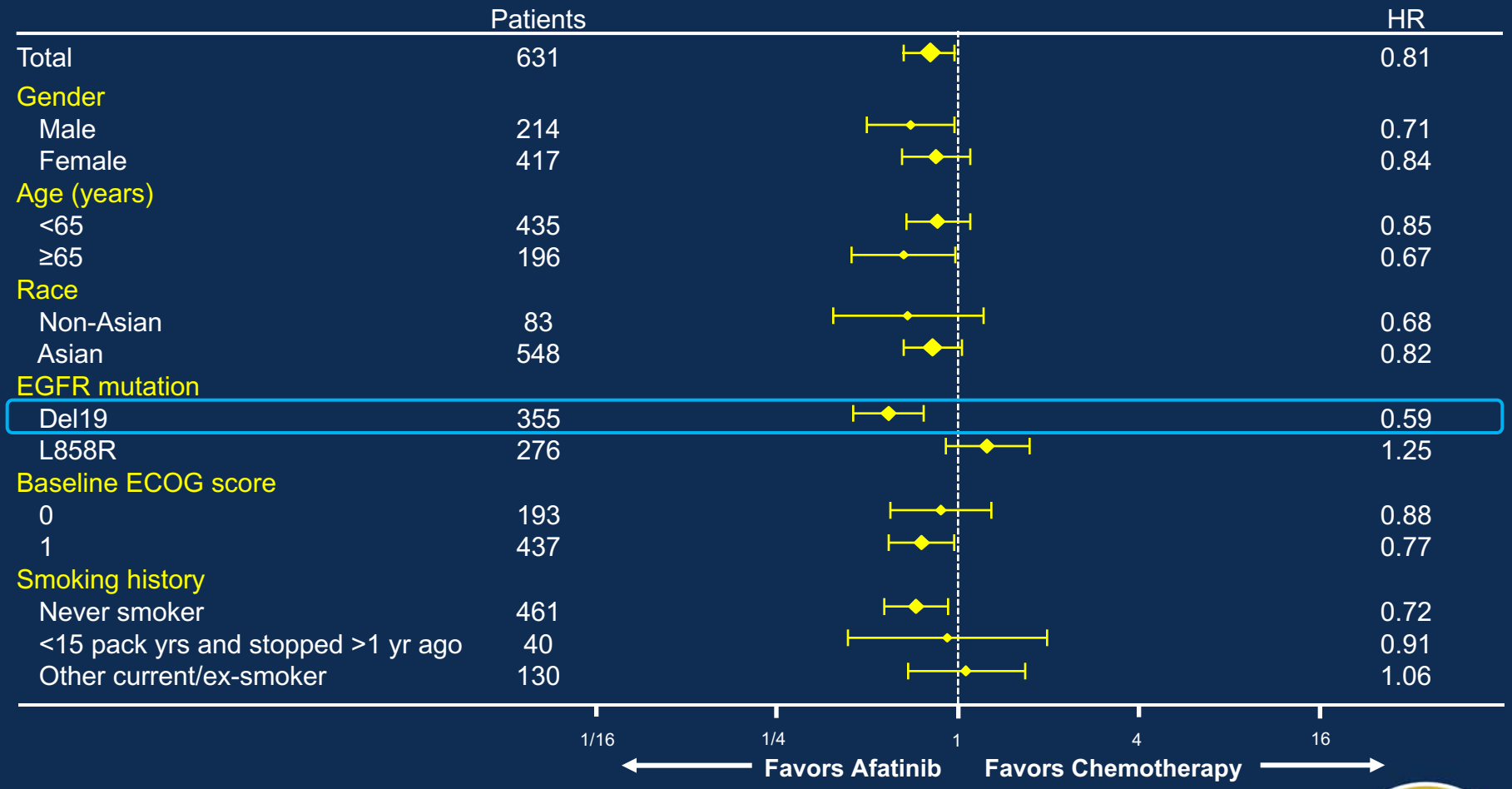


	Afatinib n=419	Chemo n=212
Median , months	**27.3**	**24.3**
HR (95%CI), p-value	**0.81** (0.66–0.99), p=0.0374	

No of patients

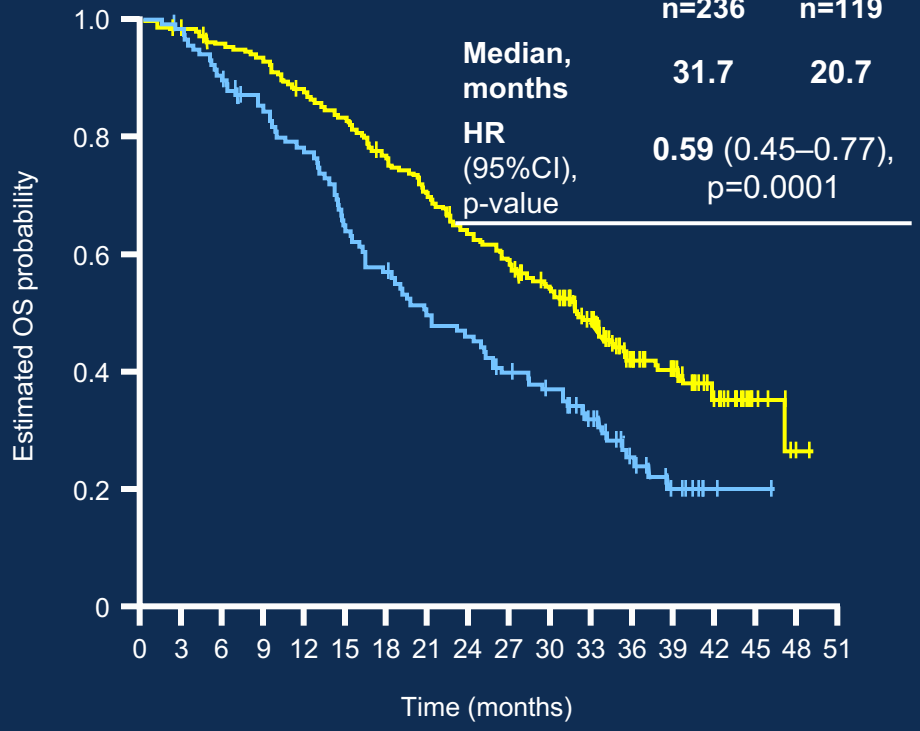
Afatinib	419	411	390	371	343	320	284	251	225	201	181	141	77	58	33	9	1	0
Chemo	212	199	185	173	162	141	124	110	101	83	70	52	34	23	10	5	1	0

Combined OS analysis in common mutations: subgroups



Combined OS analysis: mutation categories

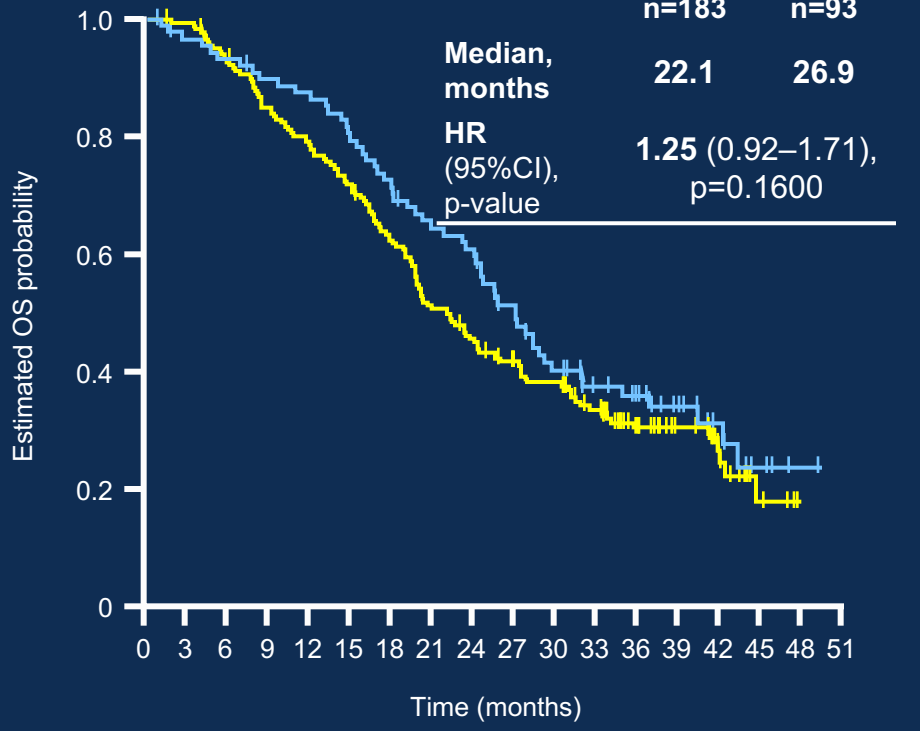
Del19



	Afatinib n=236	Chemo n=119
Median, months	31.7	20.7
HR (95%CI), p-value	**0.59** (0.45–0.77), p=0.0001	

No of patients																		
Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0

L858R



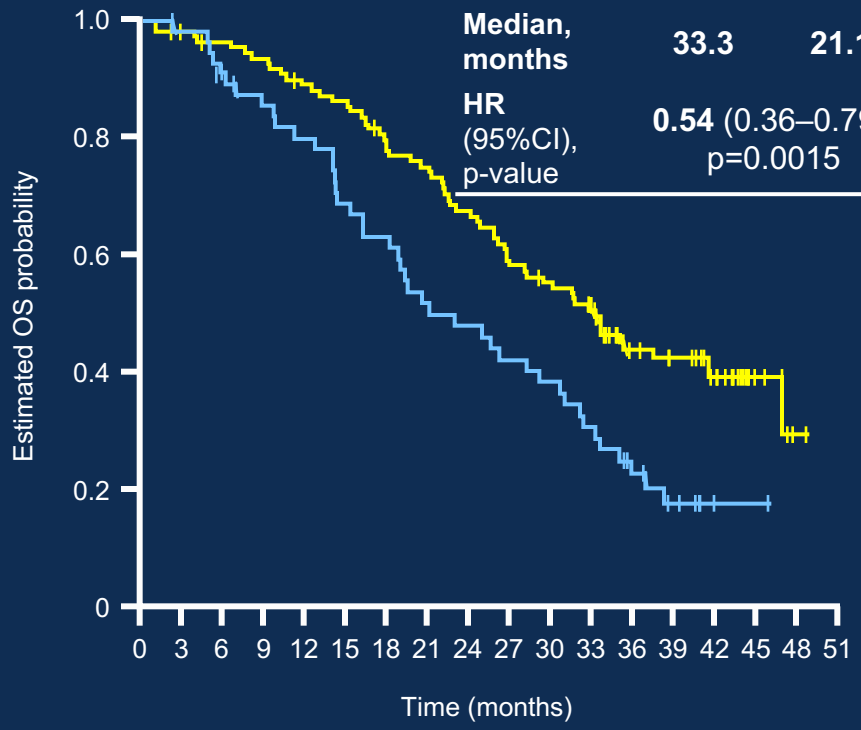
	Afatinib n=183	Chemo n=93
Median, months	22.1	26.9
HR (95%CI), p-value	**1.25** (0.92–1.71), p=0.1600	

No of patients																		
Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

OS in Del19 subgroup

LUX-Lung 3

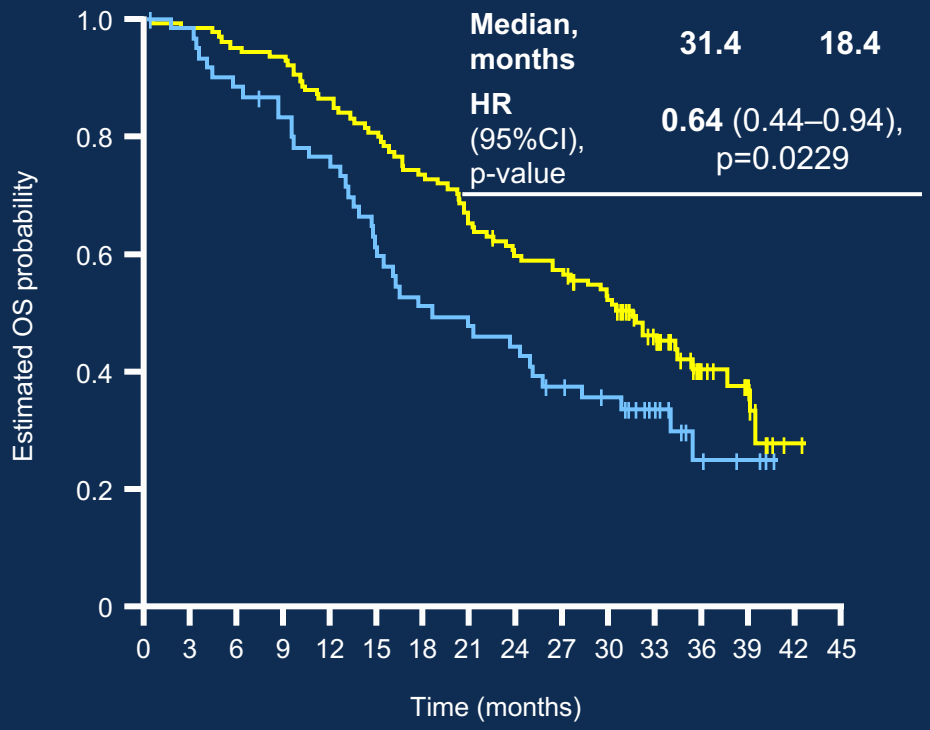
	Afatinib n=112	Pem/Cis n=57
Median, months	33.3	21.1
HR (95%CI), p-value	**0.54** (0.36–0.79), p=0.0015	



No of patients																	
Afatinib	112	108	105	102	96	93	83	80	72	62	58	51	34	30	21	6	1	0
Pem/Cis	57	55	50	46	43	37	33	27	25	22	20	16	10	6	1	1	0	0

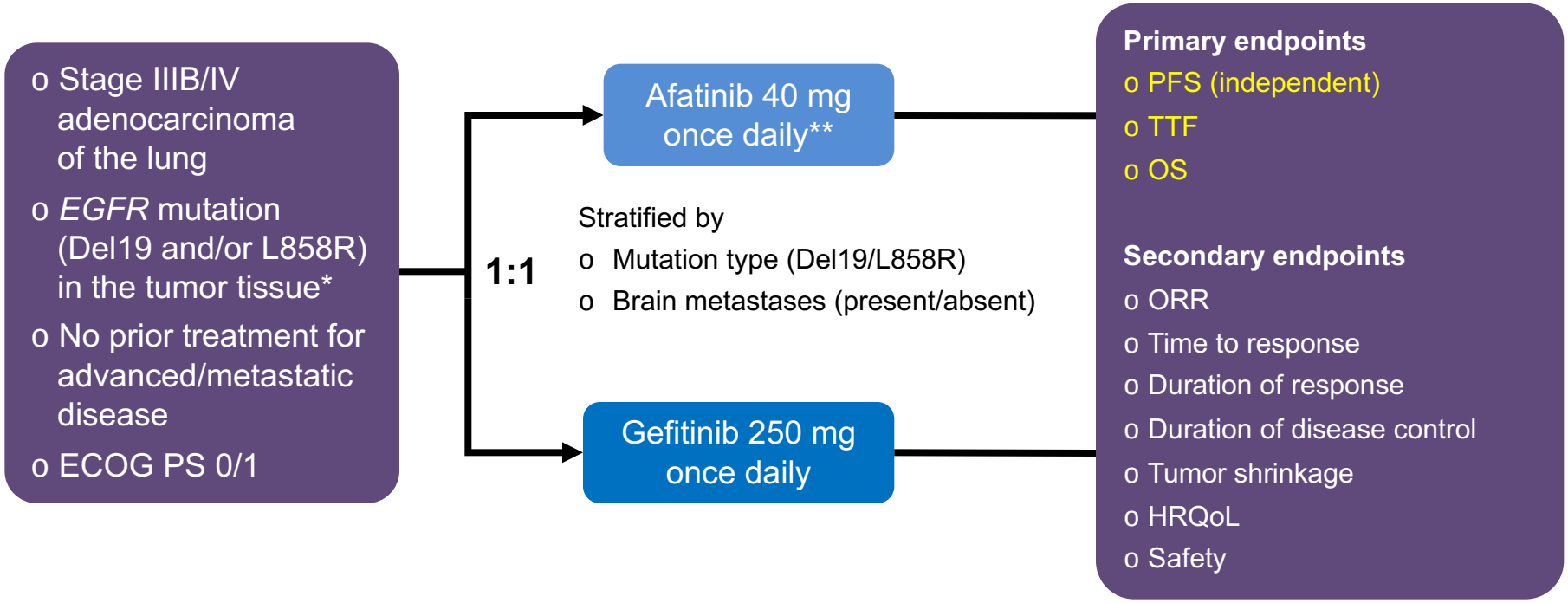
LUX-Lung 6

	Afatinib n=124	Gem/Cis n=62
Median, months	31.4	18.4
HR (95%CI), p-value	**0.64** (0.44–0.94), p=0.0229	



No of patients																
Afatinib	124	122	118	115	106	99	90	80	73	69	59	39	16	8	1	0
Gem/Cis	62	58	53	49	44	35	30	28	26	21	18	11	4	3	0	0

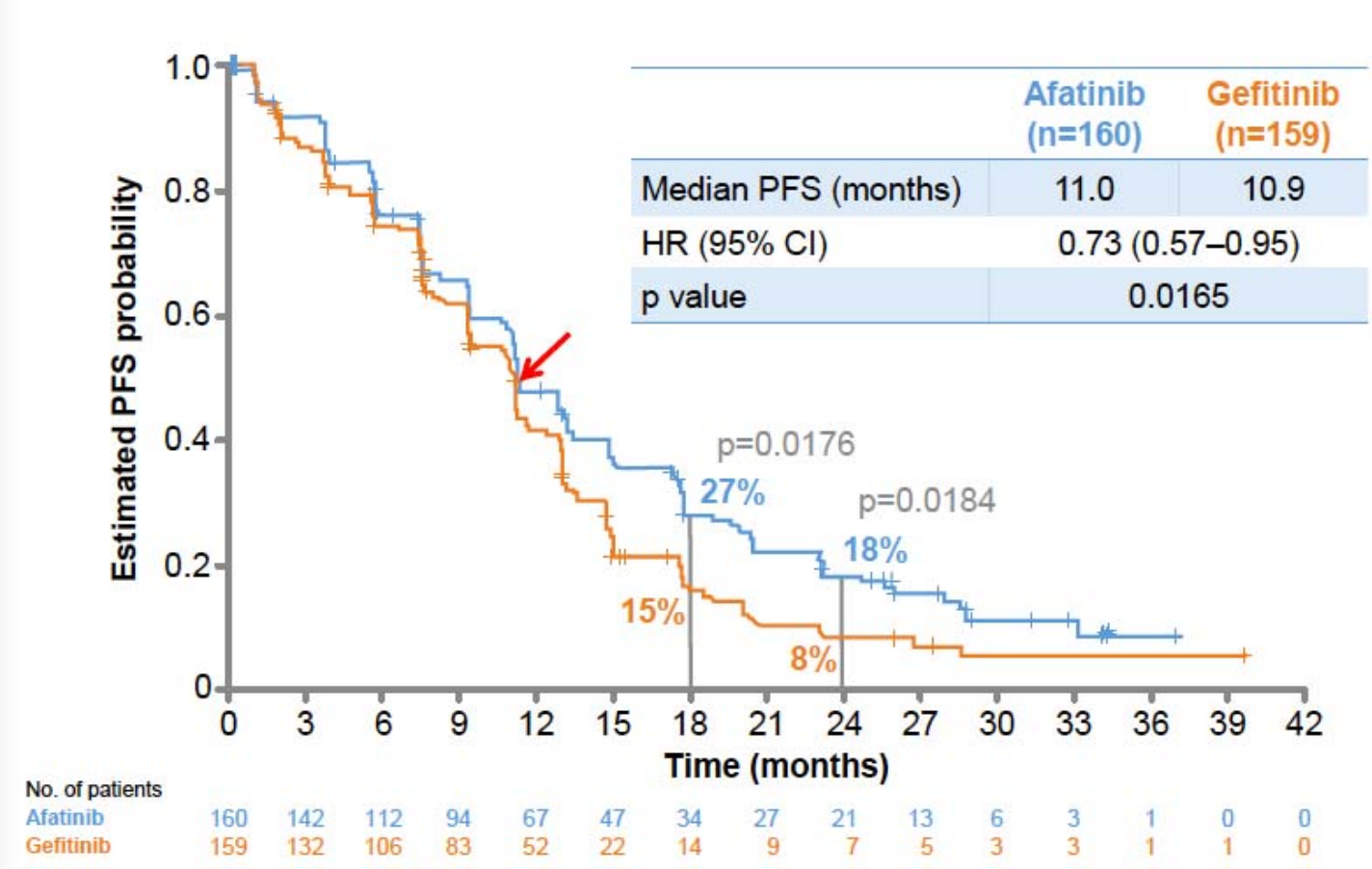
LUX-Lung 7: Study Design



- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks there after

*Central or local test
**Dose modification to 50, 30, 20 mg permitted in line with prescribing information
Adapted from Park et al, 2015.
ECOG PS, Eastern Oncology Cooperative Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time to treatment failure.

LUX-Lung 7: PFS by Independent Review[1]



	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

Final analysis for overall survival (the study's **primary endpoint**) showed no statistically significant difference in OS between afatinib (27.9 mos) and gefitinib (24.5 mos) [HR 0.86, p=0.258], including in ex19del subgroup[2]

1. Park et al, 2015.; 2. Paz-Ares, et al. ESMO 2016.

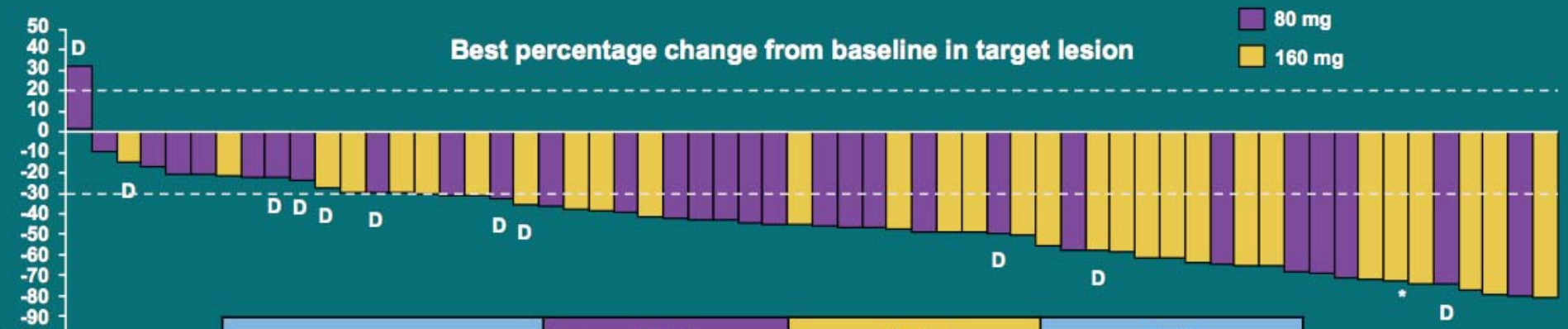
LUX-Lung 7: Overall Summary of Adverse Events

Events, %	Afatinib (n = 160)	Gefitinib (n = 159)
Any AE	98.8	100.0
Drug-related AEs	97.5	96.2
AEs leading to dose reduction*	41.9	1.9*
Drug-related AEs leading to discontinuation	6.3	6.3
Serious AEs	44.4	37.1
Drug-related serious AEs	10.6	4.4**
Drug-related fatal AEs	–	0.6***

Adapted from Park et al, 2015.
*No dose reductions foreseen for gefitinib according to prescribing information.
**Including four patients with drug-related ILD (no drug-related ILD on afatinib.
***One patient died of hepatic failure.
AE, adverse event; ILD, interstitial lung disease.

Third-Generation EGFR TKIs as First-Line Therapy

Osimertinib Response Rate in First-line Cohorts



	80 mg N=30	160 mg N=30	Total N=60
Objective response rate#	**63% (95% CI 44, 80)**	**83% (95% CI 65, 94)**	**73% (95% CI 60, 84)**
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Best objective response			
Complete response#	0	1	1
Partial response#	19	24	43
Stable disease	9	5	14
Progressive disease	2	0	2

Population: evaluable for response, data cut-off April 15, 2015
Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), programmatically calculated from investigator-recorded tumor measurement

Update at ELCC 2016: ORR 77%, median PFS NR (80 mg dose), median PFS 19.3 mos (160 mg dose)

Ramalingam et al, ASCO 2015 and Ramalingam et al., ELCC 2016.

Summary

- EGFR TKIs are established first-line therapy for metastatic EGFR mutant NSCLC
- First line EGFR TKI options in the US include gefitinib, erlotinib, and afatinib
- Combined LUX-Lung 3 and 6 OS analysis demonstrated an OS benefit in EGFR ex19del patients
- However, final OS analysis of LUX-Lung 7 (afatinib vs gefitinib) showed no statistically significant difference in OS (including in ex19del subgroup)
- Toxicities vary among the different EGFR TKIs
- Selection ultimately tailored to each individual patient