NEWEVIDENCE

Afatinib versus gefitinib as first-line treatment for patients with advanced non-small cell lung cancer harboring activating EGFR mutations: LUX-Lung 7

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Disclosures

- Employment: Samsung Medical Center
- Advisory Boards: Boehringer Ingelheim (uncompensated)

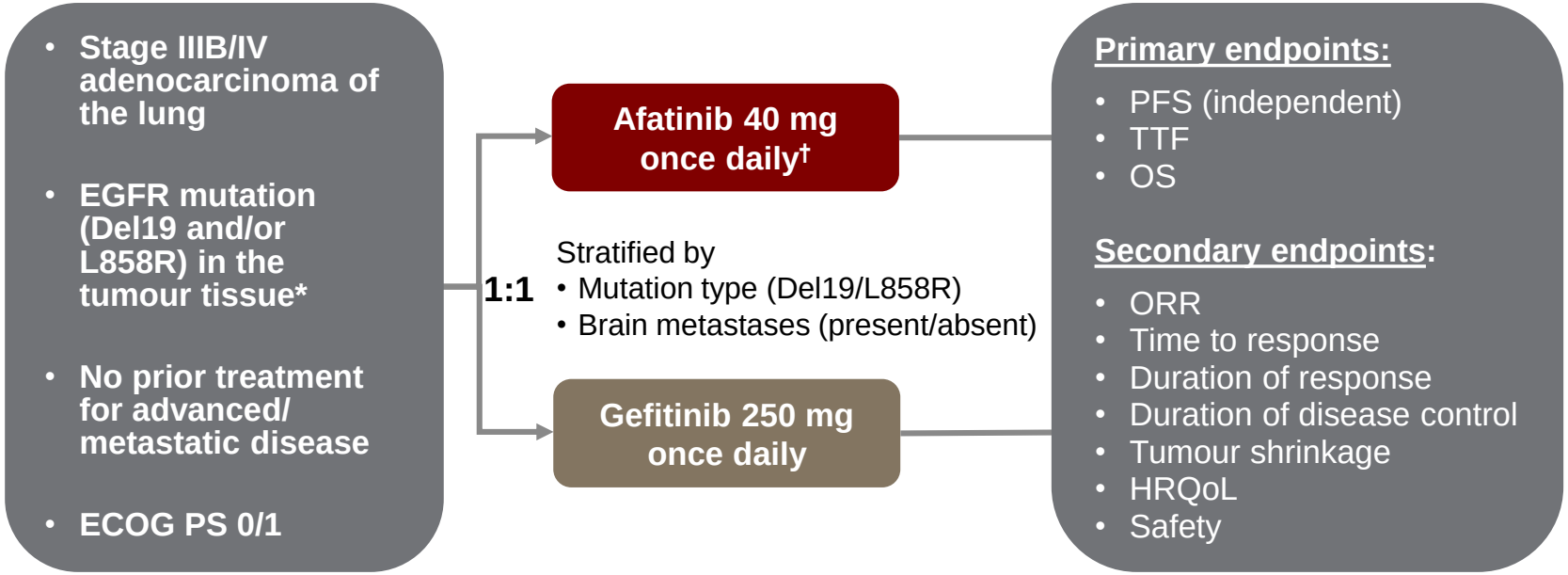
Background

- Afatinib and other EGFR-targeting agents, erlotinib and gefitinib, are approved first-line treatments for EGFR M+ NSCLC[1]
- Afatinib (second-generation TKI) irreversibly inhibits signaling of EGFR, HER2-HER4, whereas gefitinib and erlotinib (first-generation TKIs) reversibly inhibit EGFR[2–4]
- LUX-Lung 7 is the first prospective global randomized trial evaluating two EGFR-directed therapies in patients with EGFR M+ NSCLC

1. Sebastian M, et al. Eur Respir Rev 2014;23:92–105.
2. Costanzo R, et al. Expert Rev Anticancer Ther 2013;13(10):1207–18.
3. Li D, et al. Oncogene 2008;27:4702–11.
4. Solca F, et al. J Pharmacol Exp Ther 2012;343:342–50.

EGFR = epidermal growth factor receptor; M+ = mutation-positive; HER = human epidermal growth factor receptor; NSCLC = non-small cell lung cancer; TKI = tyrosine kinase inhibitor

Study Design



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

* Central or local test.
† Dose modification to 50 mg, 30 mg, and 20 mg permitted in line with prescribing information.

Del19 = exon 19 deletions; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; L858R = exon 21 L858R point mutation; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors; TTF = time to treatment failure

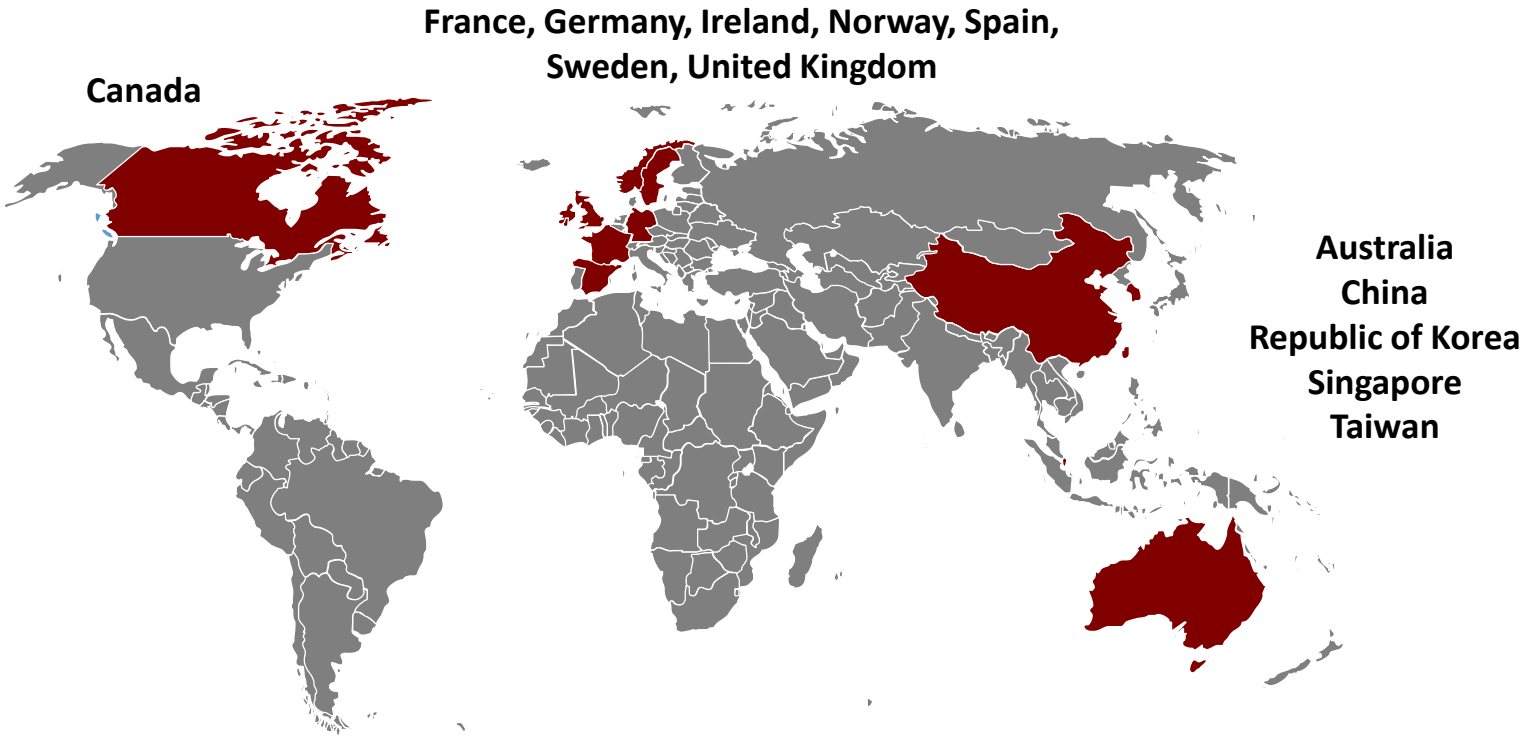
Statistical Design

- Main study objective: to estimate the HR for PFS, TTF, and OS* on afatinib, relative to gefitinib
- Sample size was based on controlling the width of the 95% CI for the PFS HR, allowing for a width of ±0.25 on the log scale after observing 250 events
- All statistical testing was at two-sided 5% alpha level with no adjustment for multiplicity
- Time-to-event endpoints were analyzed via stratified Cox-regression analysis and log-rank test

* At the time of PFS analysis, OS endpoint is still immature.

CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure

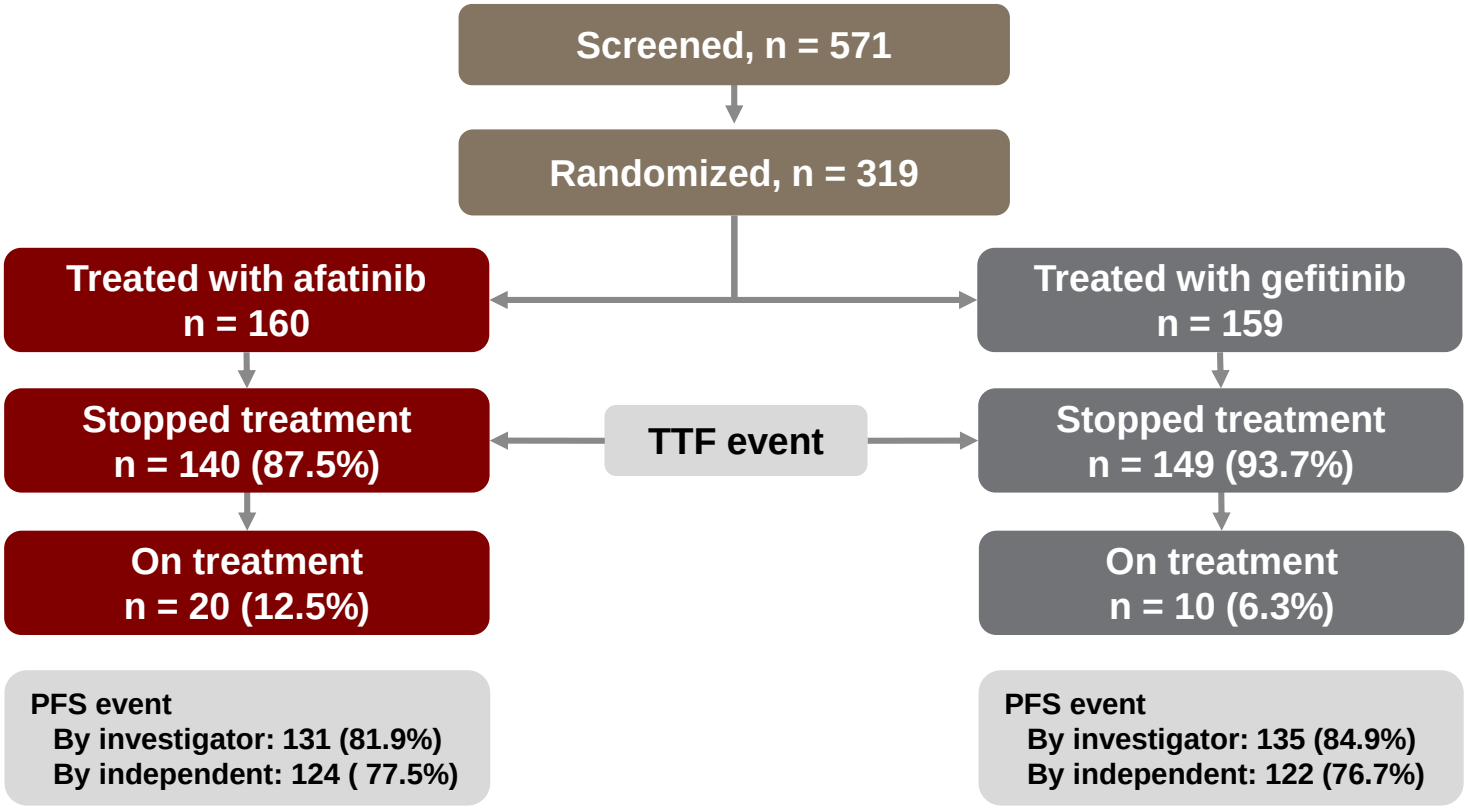
Study Conduct:
64 Sites / 13 Countries



- Recruitment: December 2011–August 2013
- Median follow-up for PFS: 27.3 months

PFS = progression-free survival

Patient Disposition



As of August 21, 2015

PFS = progression-free survival; TTF = time to treatment failure

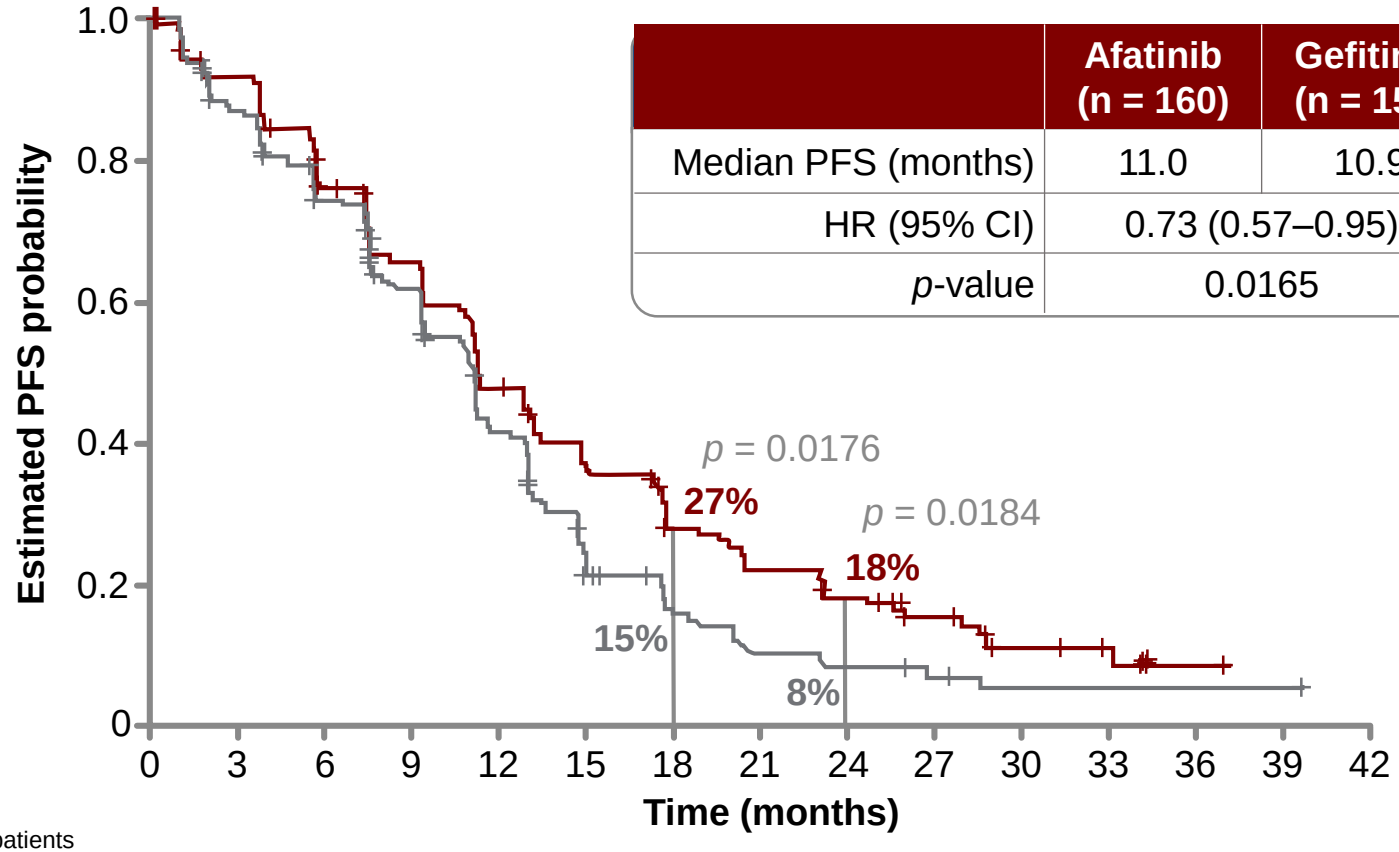
Baseline Characteristics

		Afatinib (n = 160)	Gefitinib (n = 159)
Median age, years (range)		63 (30–86)	63 (32–89)
Gender, %	Female / Male	57 / 43	67 / 33
Race, %	Asian Non-Asian	59 41	55 45
Brain metastases*, %		16	16
Smoking status, %	Never smoked Light ex-smoker Current / other ex-smoker	66 13 21	67 12 21
Baseline ECOG PS, %	0 1	32 68	30 70
NSCLC stage, %	IIIB IV	5 95	2 98
EGFR mutation, %	Del19 L858R	58 42	58 42

* Stable brain metastases: Incidentally found asymptomatic brain metastases not requiring any local brain radiation and steroid therapy. Asymptomatic brain metastases previously radiated and >1 week off corticosteroids and/or anti-convulsants treatment before study randomization. Concomitant brain radiation not allowed.

Del19 = exon 19 deletions; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; L858R = exon 21 L858R point mutation; NSCLC = non-small cell lung cancer

PFS by Independent Review



	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	

No. of patients															
Afatinib	160	142	112	94	67	47	34	27	21	13	6	3	1	0	0
Gefitinib	159	132	106	83	52	22	14	9	7	5	3	3	1	1	0

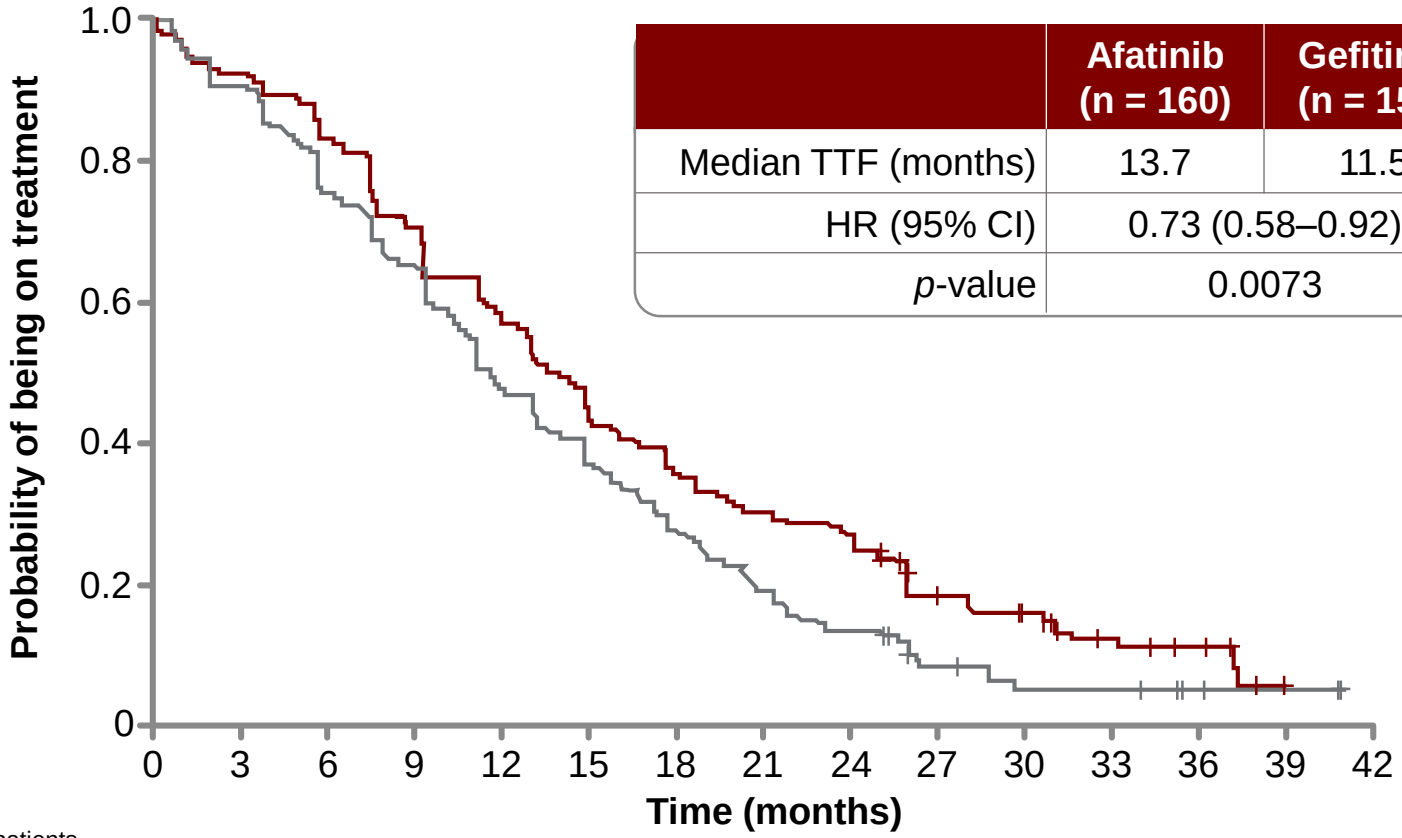
CI = confidence interval; HR = hazard ratio; PFS = progression-free survival

PFS in Prospectively Defined Subgroups

Factors		N	PFS	HR (95% CI)
Total		319		0.73 (0.57–0.95)
EGFR mutation	L858R	133		0.71 (0.48–1.06)
	Del19	186		0.76 (0.55–1.06)
Brain metastases	Absent	268		0.74 (0.56–0.98)
	Present	51		0.76 (0.41–1.44)
Baseline ECOG PS	0	98		0.89 (0.54–1.47)
	1	221		0.71 (0.52–0.95)
Gender	Male	122		0.88 (0.59–1.31)
	Female	197		0.65 (0.47–0.91)
Age	<65 years	177		0.68 (0.48–0.97)
	≥65 years	142		0.85 (0.59–1.22)
Race	Non-Asian	137		0.72 (0.49–1.06)
	Asian	182		0.76 (0.54–1.06)
Smoking history	Never smoked	212		0.80 (0.58–1.10)
	Light ex-smoker	40		1.09 (0.56–2.14)
	Current or other ex-smokers	67		0.48 (0.27–0.85)

CI = confidence interval; Del19 = exon 19 deletions; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HR = hazard ratio; L858R = exon 21 L858R point mutation; PFS = progression-free survival

Time to Treatment Failure

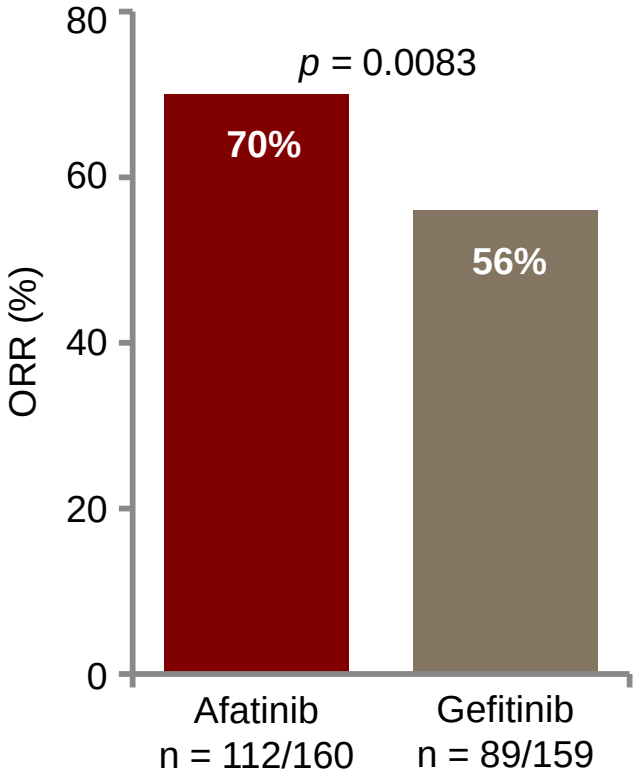


	Afatinib (n = 160)	Gefitinib (n = 159)
Median TTF (months)	13.7	11.5
HR (95% CI)	0.73 (0.58–0.92)	
p-value	0.0073	

No. of patients															
Afatinib	160	148	133	113	91	68	56	48	40	25	18	9	5	0	0
Gefitinib	159	144	120	103	74	59	43	30	21	11	6	6	2	2	0

CI = confidence interval; HR = hazard ratio; TTF = time to treatment failure

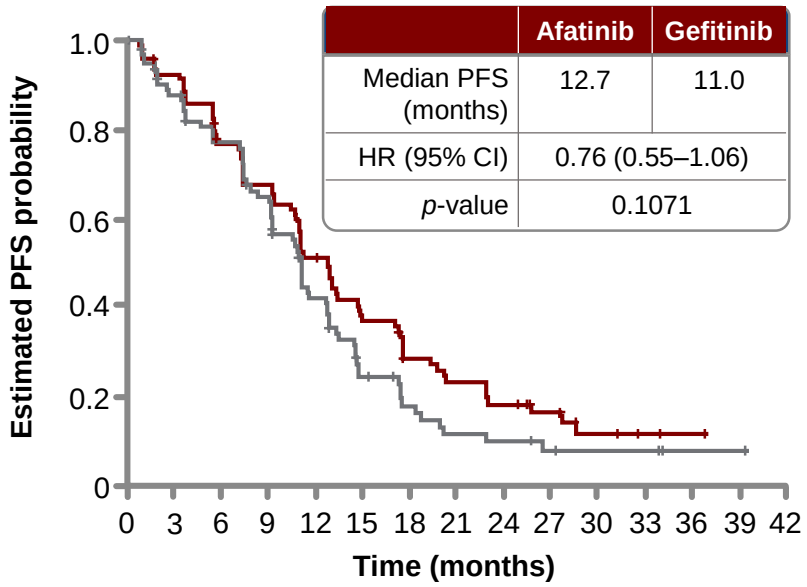
Objective Response and Duration of Response (Independent Review)



	Afatinib (n = 112)	Gefitinib (n = 89)
Median DoR (months)	10.1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

CI = confidence interval; DoR = duration of response; ORR = objective response rate

Efficacy in Patients With Del19 Mutation

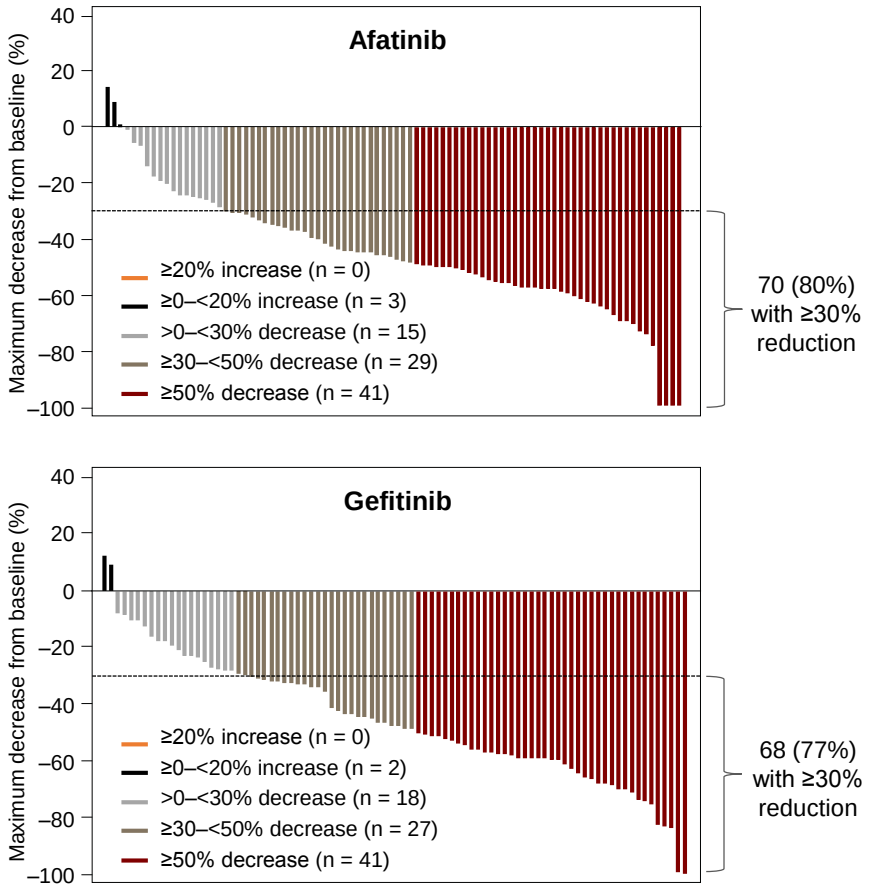


	Afatinib	Gefitinib
Median PFS (months)	12.7	11.0
HR (95% CI)	0.76 (0.55–1.06)	
p-value	0.1071	

No. of patients

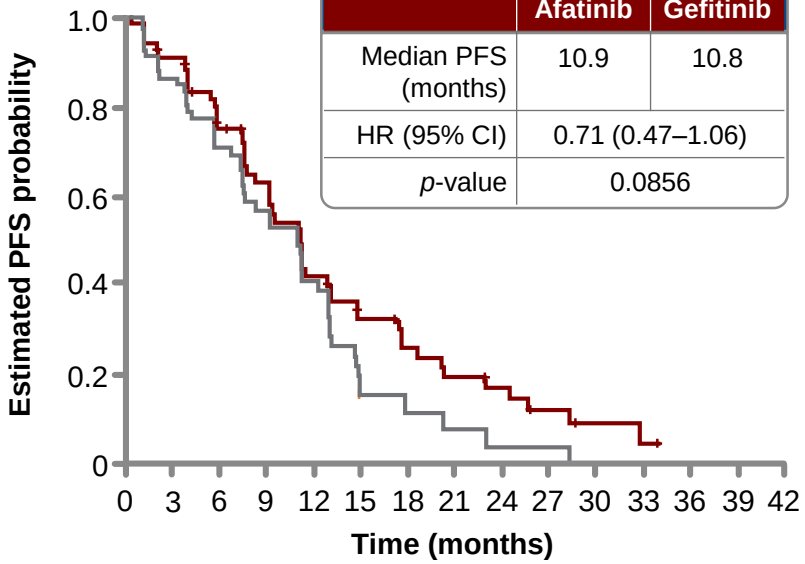
Afatinib	93	83	67	58	43	31	22	18	14	9	4	2	1	0	0
Gefitinib	93	76	64	53	32	17	11	7	6	4	3	3	1	1	0

	Afatinib (n = 93)	Gefitinib (n = 93)
ORR	73%	66%



CI = confidence interval; Del19 = exon 19 deletions; HR = hazard ratio; ORR = objective response rate; PFS = progression-free survival

Efficacy in Patients With L858R Mutation

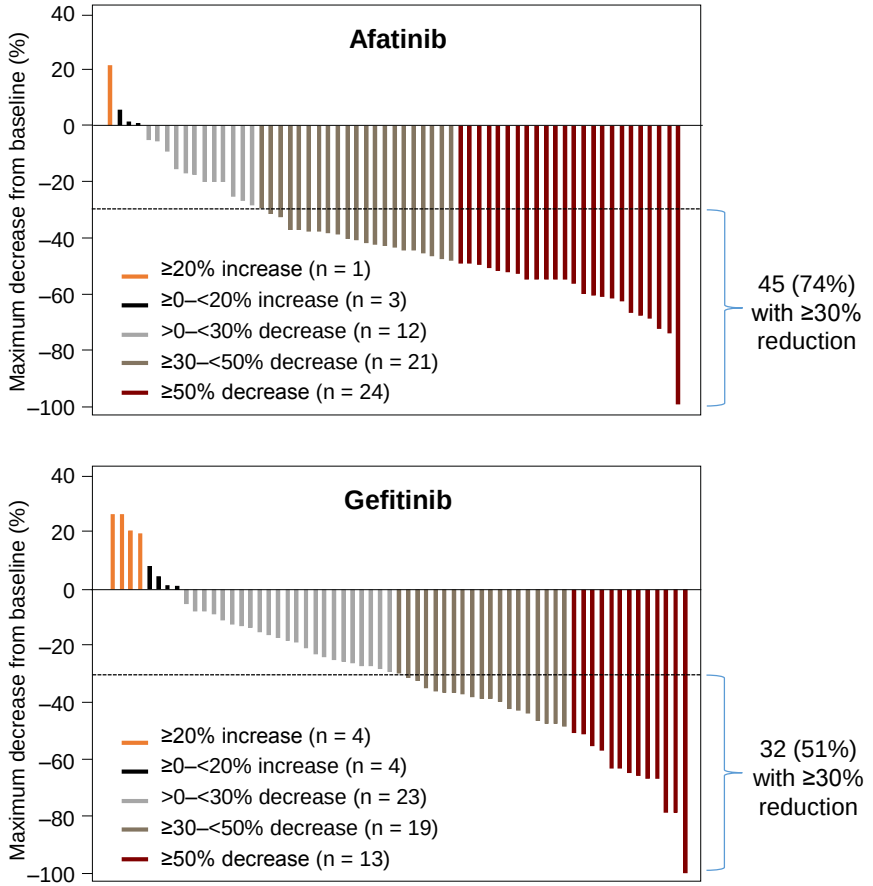


	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p-value	0.0856	

No. of patients

Afatinib	67	59	45	36	24	16	12	9	7	4	2	1	0	0	0
Gefitinib	66	56	42	30	20	5	3	2	1	1	0	0	0	0	0

	Afatinib (n = 67)	Gefitinib (n = 66)
ORR	66%	42%



CI = confidence interval; HR = hazard ratio; L858R = exon 21 L858R point mutation; ORR = objective response rate; PFS = progression-free survival

Overall Summary of AEs

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 AE	-	0.6‡

* 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

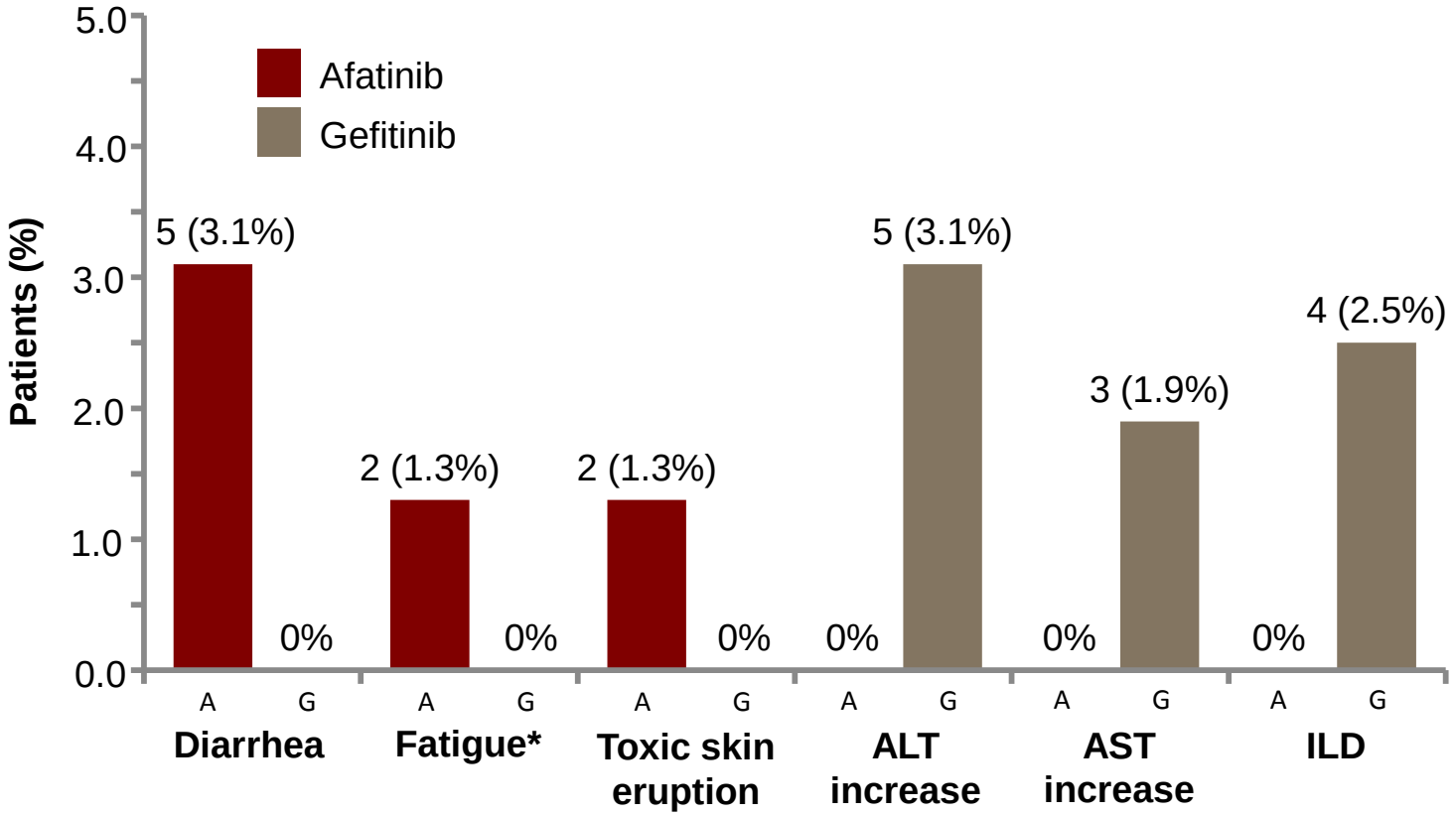
Drug-Related AEs (>10%)

AE category, %	Afatinib (n = 160)		Gefitinib (n = 159)	
	All	Grade 3	All	Grade 3
Diarrhea	90.0	11.9†	61.0	1.3
Rash/acne*	88.8	9.4	81.1	3.1
Stomatitis*	64.4	4.4	23.9	-
Paronychia*	55.6	1.9	17.0	0.6
Dry skin	32.5	-	37.1	-
Pruritus	23.1	-	22.6	-
Fatigue*	20.6	5.6	14.5	-
Decreased appetite	16.3	0.6	11.9	-
Nausea	16.3	1.3	13.8	-
Alopecia	10.6	-	15.1	-
Vomiting	10.6	-	3.8	0.6
ALT increased	9.4	-	23.9	7.5‡
AST increased	6.3	-	20.8	2.5

* Grouped terms of AEs.
† Plus one case of grade 4 diarrhea.
‡ Plus one case of grade 4 increased ALT.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Drug-Related AEs Leading to Discontinuation in >1 Patient



* Grouped terms of AEs.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = interstitial lung disease

Summary and Conclusion

- Afatinib significantly improved PFS of patients with EGFR M+ NSCLC relative to gefitinib. Results are consistent across subgroups
- Afatinib treatment was associated with a significant improvement in response rate and TTF
- Improvement in efficacy was observed in both Del19 and L858R populations
- OS data were immature (current HR: 0.87, 95% CI: 0.66–1.15)
- AEs in both groups were consistent with previous experience and were manageable, leading to equally low rates of treatment discontinuation
- LUX-Lung 7 confirms the benefit of irreversible ErbB blockade with afatinib over reversible EGFR inhibition with gefitinib in treatment of EGFR M+ NSCLC

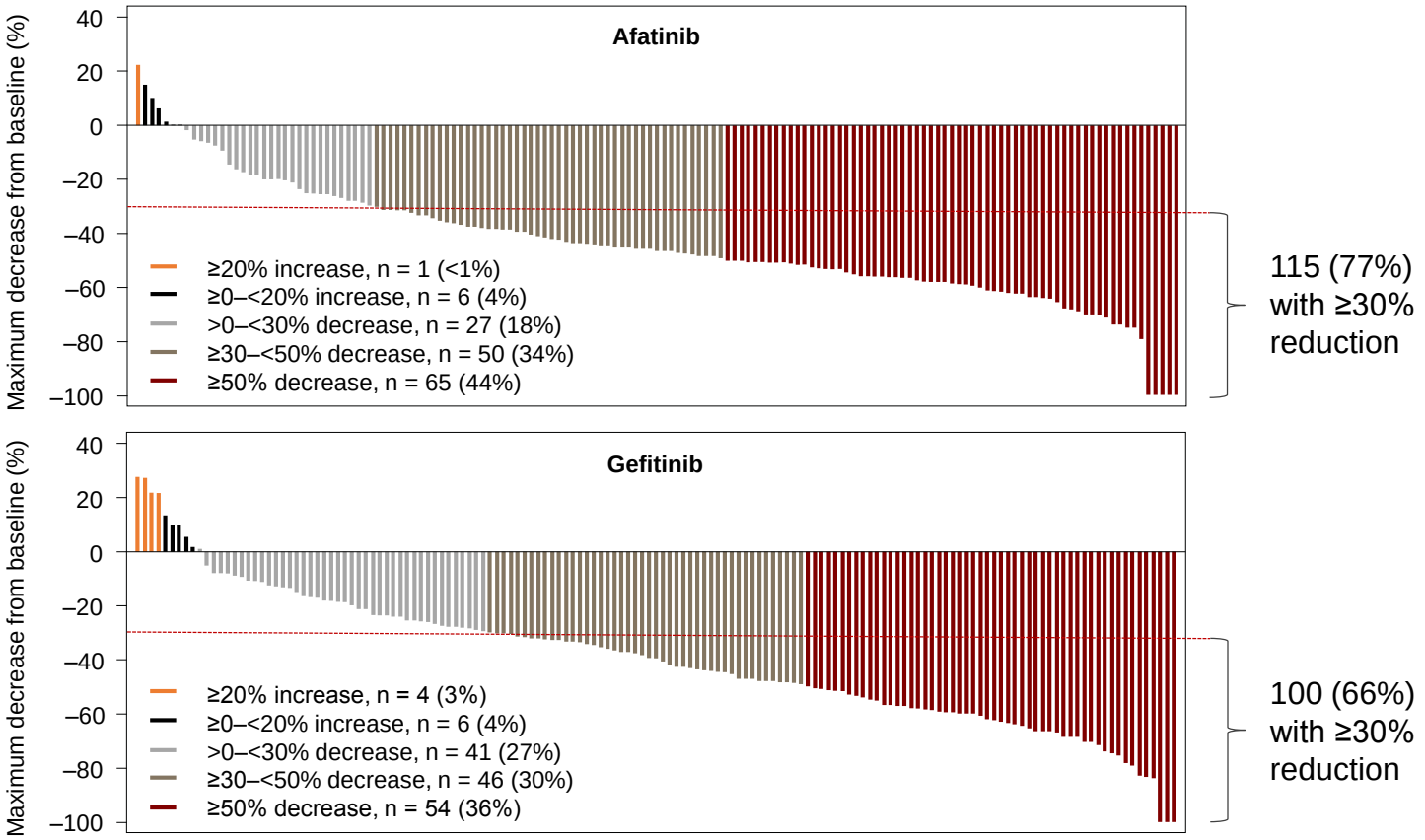
AE = adverse event; CI = confidence interval; Del19 = exon 19 deletions; EGFR = epidermal growth factor receptor; ErbB = erythroblastic leukemia viral oncogene; HR = hazard ratio; L858R = exon 21 L858R point mutation; M+ = mutation-positive; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure

Acknowledgments

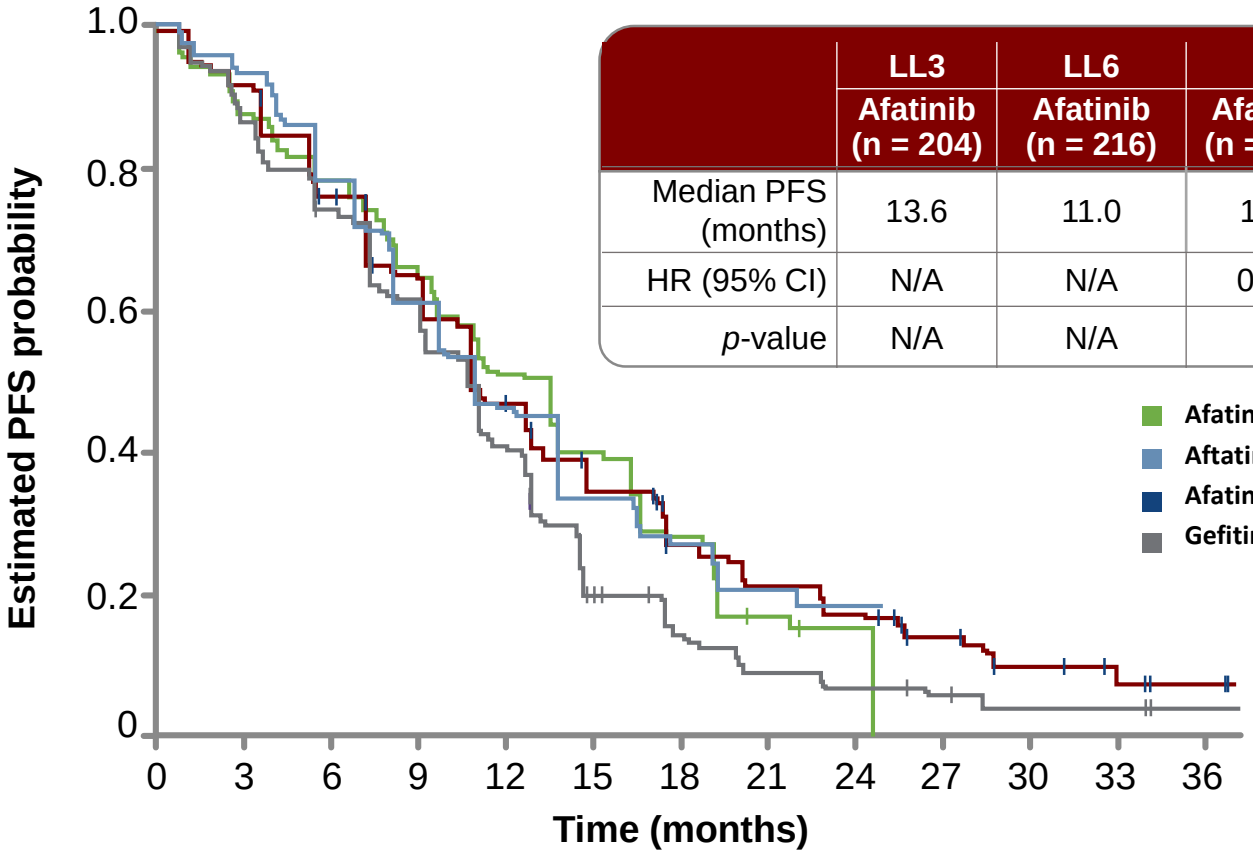
Thank you to all of the patients and their families, and the LUX-Lung 7 study investigators and their teams for participating in this study

Back-Up

Tumour Shrinkage (Independent Review)



PFS With TKI in Common Mutation: LUX-Lung 3/6 and LUX-Lung 7



	LL3	LL6	LL7	
	Afatinib (n = 204)	Afatinib (n = 216)	Afatinib (n = 160)	Gefitinib (n = 159)
Median PFS (months)	13.6	11.0	11.0	10.9
HR (95% CI)	N/A	N/A	0.73 (0.57–0.95)	
p-value	N/A	N/A	0.0165	

CI = confidence interval; HR = hazard ratio; N/A = not applicable; PFS = progression-free survival