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

- Advisor/Consultant ;

  Boehringer Ingelheim (uncompensated)

  Astellas, Astra-Zeneca, Clovis, Eli Lilly, GSK, Hanmi, Kyowa Hakko Kirin, Novartis, ONO Pharm, Pfizer, Roche, Takeda Millenium

- Research Fund; Astra-Zeneca

Background

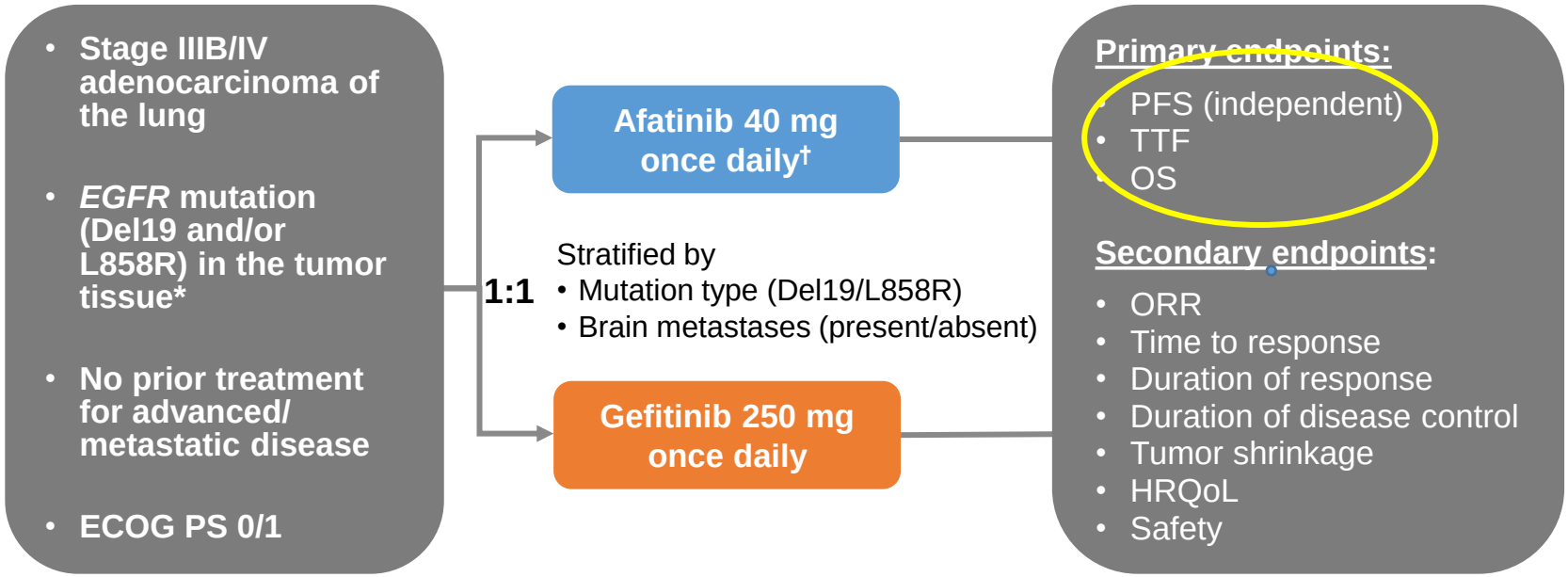
- Afatinib and other EGFR-targeting agents, erlotinib and gefitinib, are approved first-line treatments for *EGFR*m+ NSCLC[1]

- Afatinib irreversibly inhibits signaling of EGFR, HER2-HER4 *(2nd generation TKI)*, whereas gefitinib and erlotinib reversibly inhibit EGFR *(1st generation TKIs)*[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*m+, *EGFR* mutation-positive; HER, human epidermal growth factor receptor; TKI, tyrosine kinase inhibitor

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 thereafter

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

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

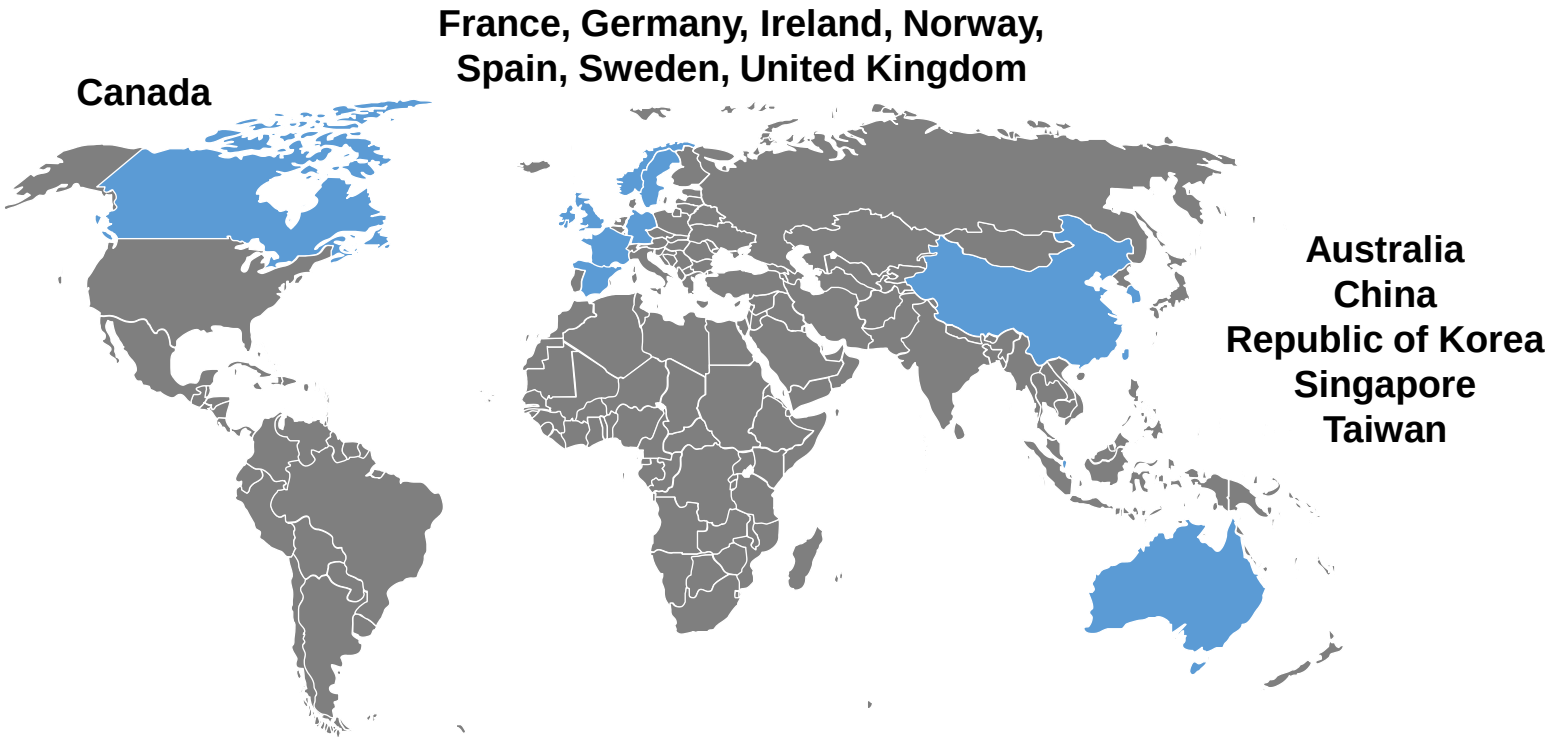
Statistical design

- Main study objective: to estimate the hazard ratio (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 at two-sided 5% alpha level with no adjustment for multiplicity
- Time-to-event endpoints analyzed via stratified Cox-regression analysis and log-rank test

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

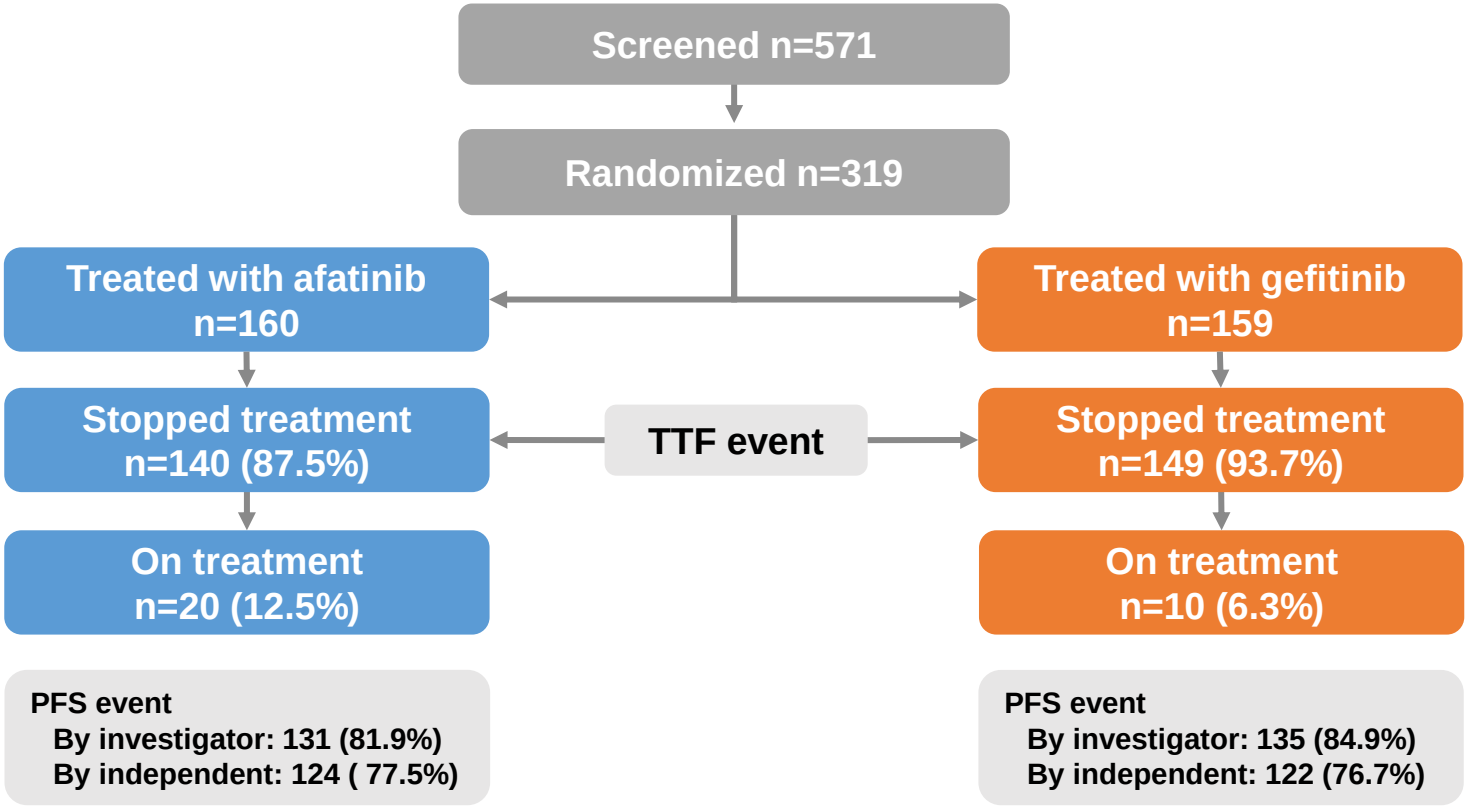
CI, confidence interval

Study conduct:
64 sites/13 countries



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

Patient disposition



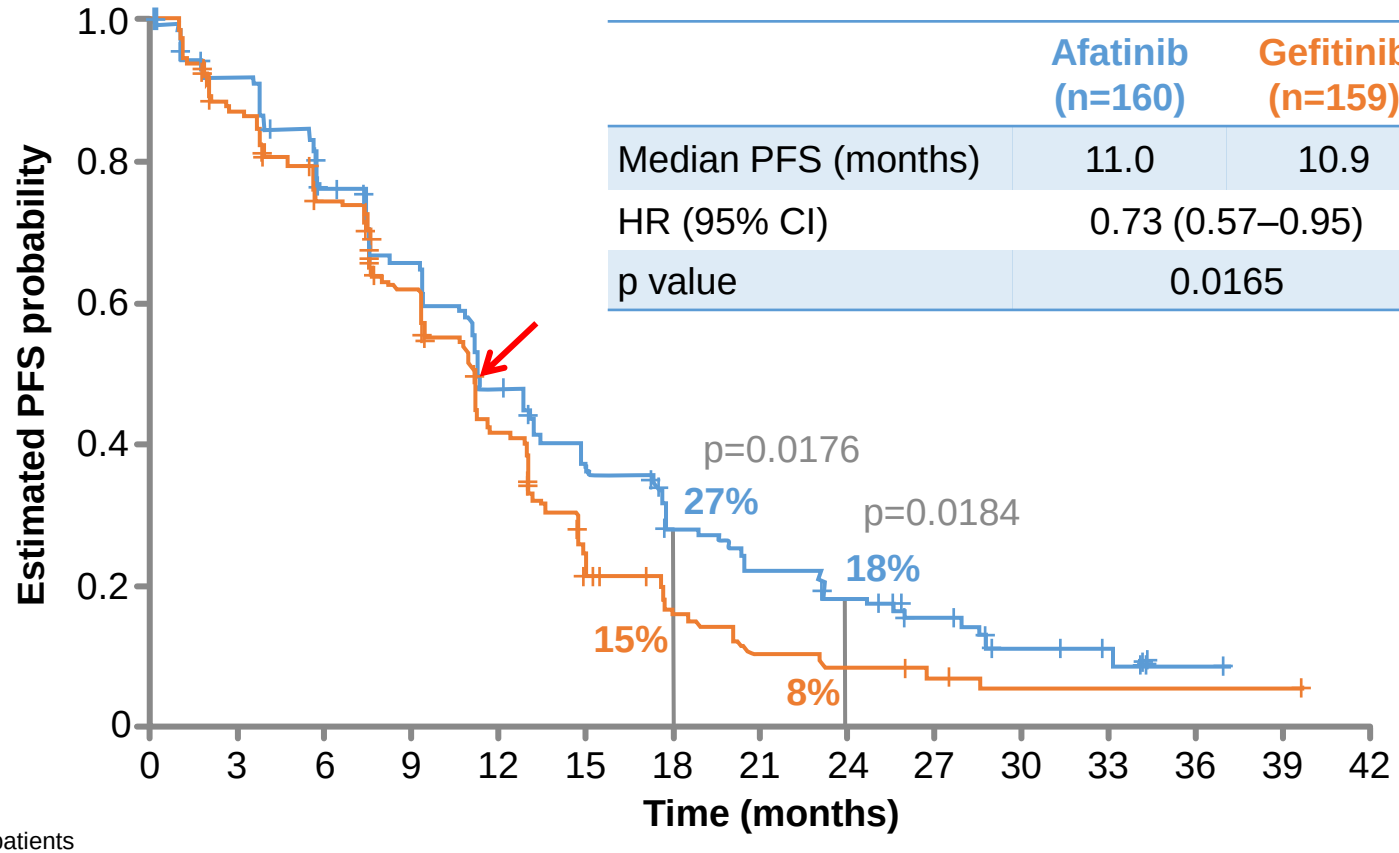
As of 21 August 2015

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, %	**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.

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	

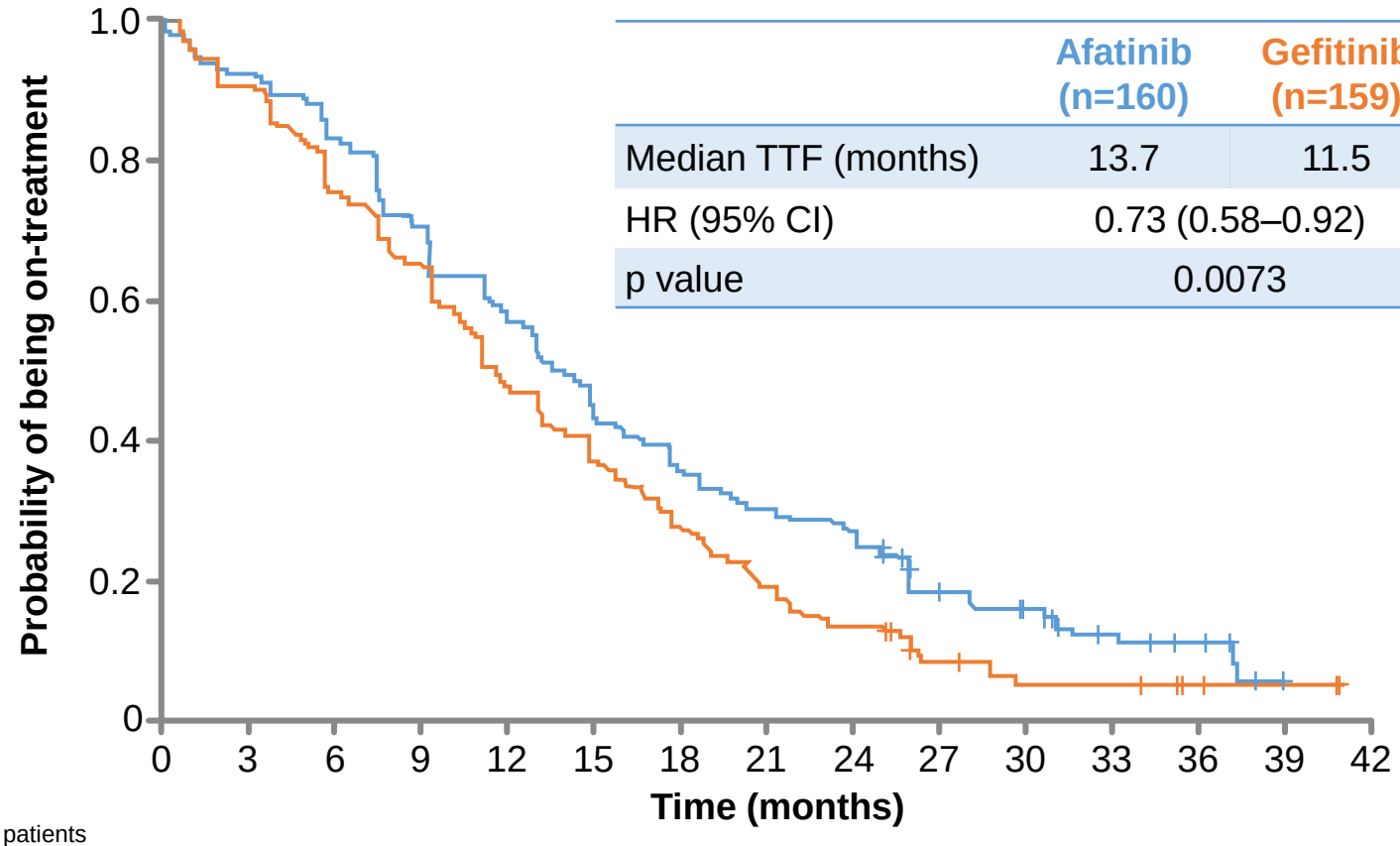
No. of patients

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

PFS in prospectively defined subgroups

Factors		N	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 score	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)

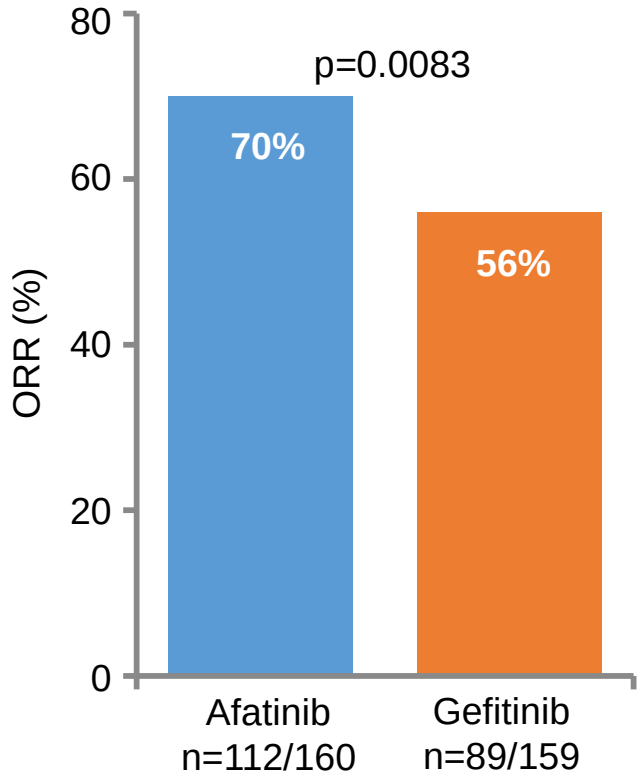
Time to treatment failure



	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

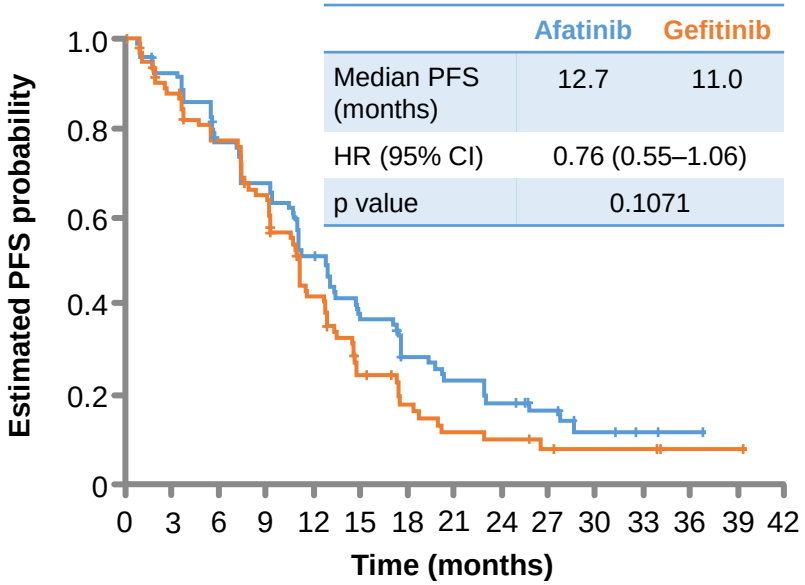
Objective response and duration of response (independent review)



	Afatinib (n=112)	Gefitinib (n=89)
Median DoR (months)	10 .1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

DoR, duration of response

Efficacy in patients with Del19 mutation

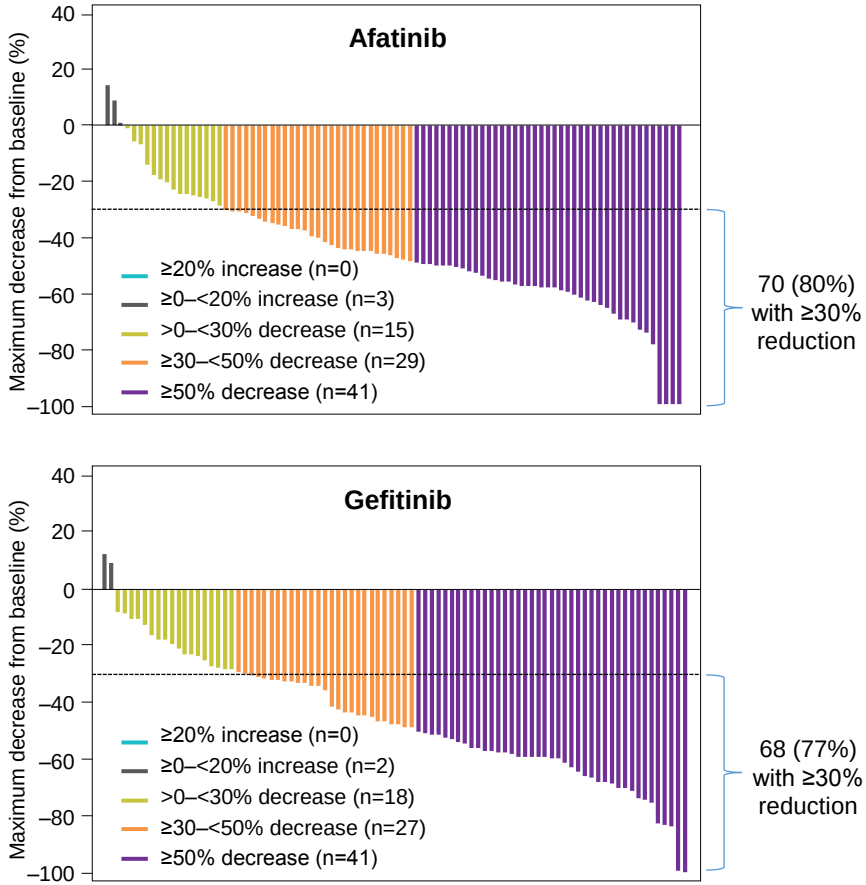


	Afatinib	Gefitinib
Median PFS (months)	12.7	11.0
HR (95% CI)	0.76 (0.55–1.06)	
p value	0.1071	

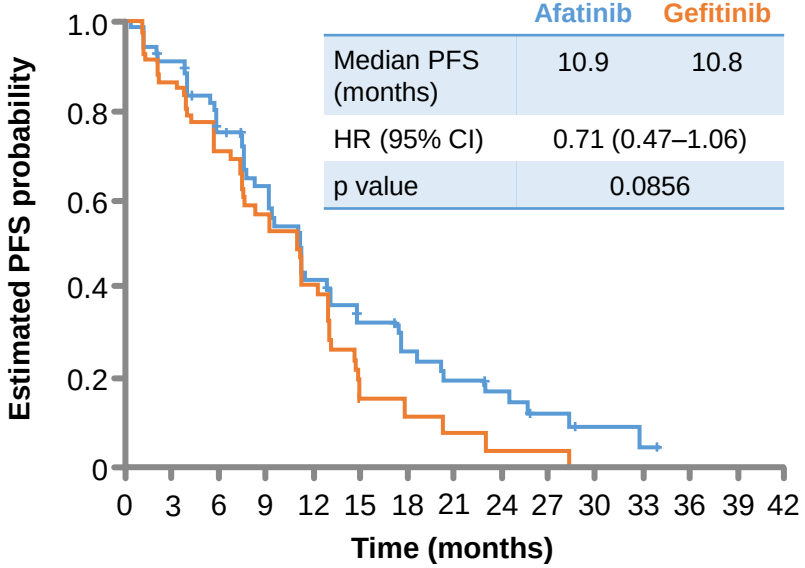
No. of patients

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%



Efficacy in patients with L858R mutation

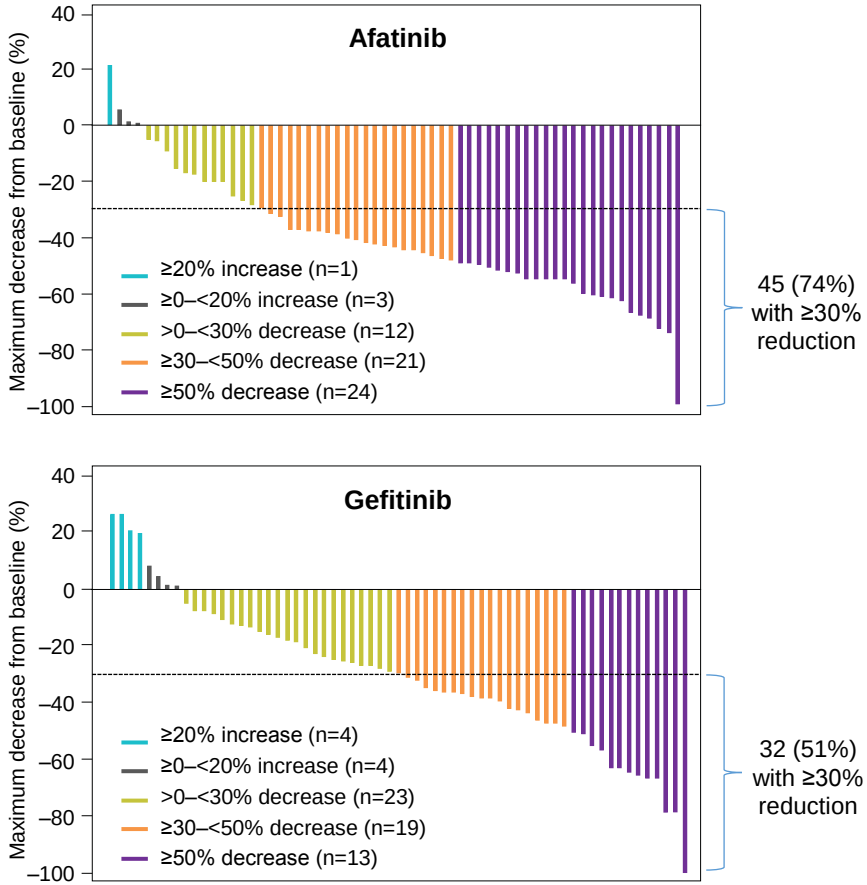


	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p value	0.0856	

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%



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

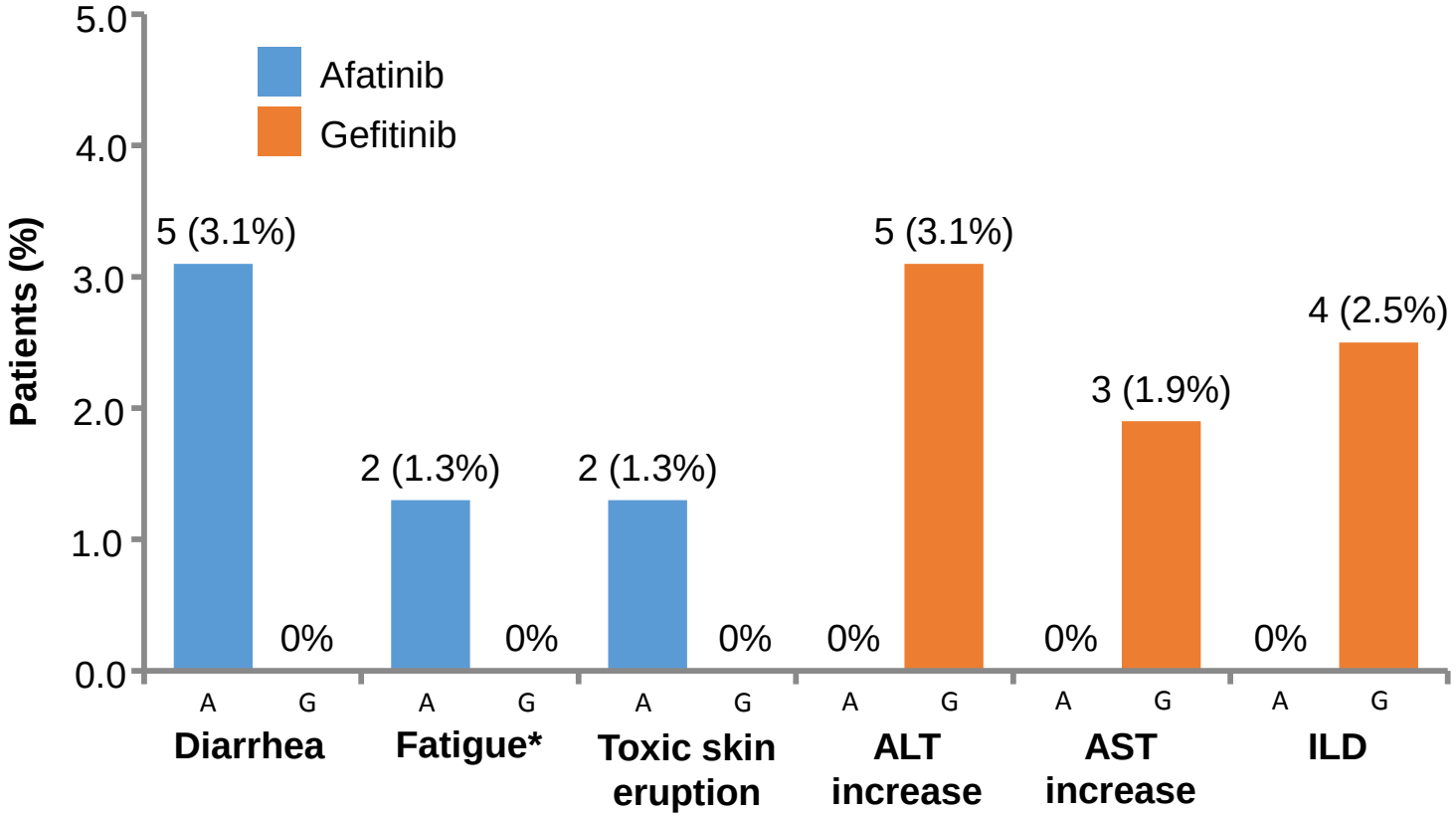
Drug-related AEs (>10%)

	Afatinib (n=160)		Gefitinib (n=159)	
AE category, %	**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 1 case of grade 4 diarrhea
‡Plus 1 case of grade 4 increased ALT
ALT, alanine aminotransferase; AST, aspartate aminotransferase

Drug-related AEs leading to discontinuation in >1 patient



*Grouped terms of AEs

Summary and conclusion

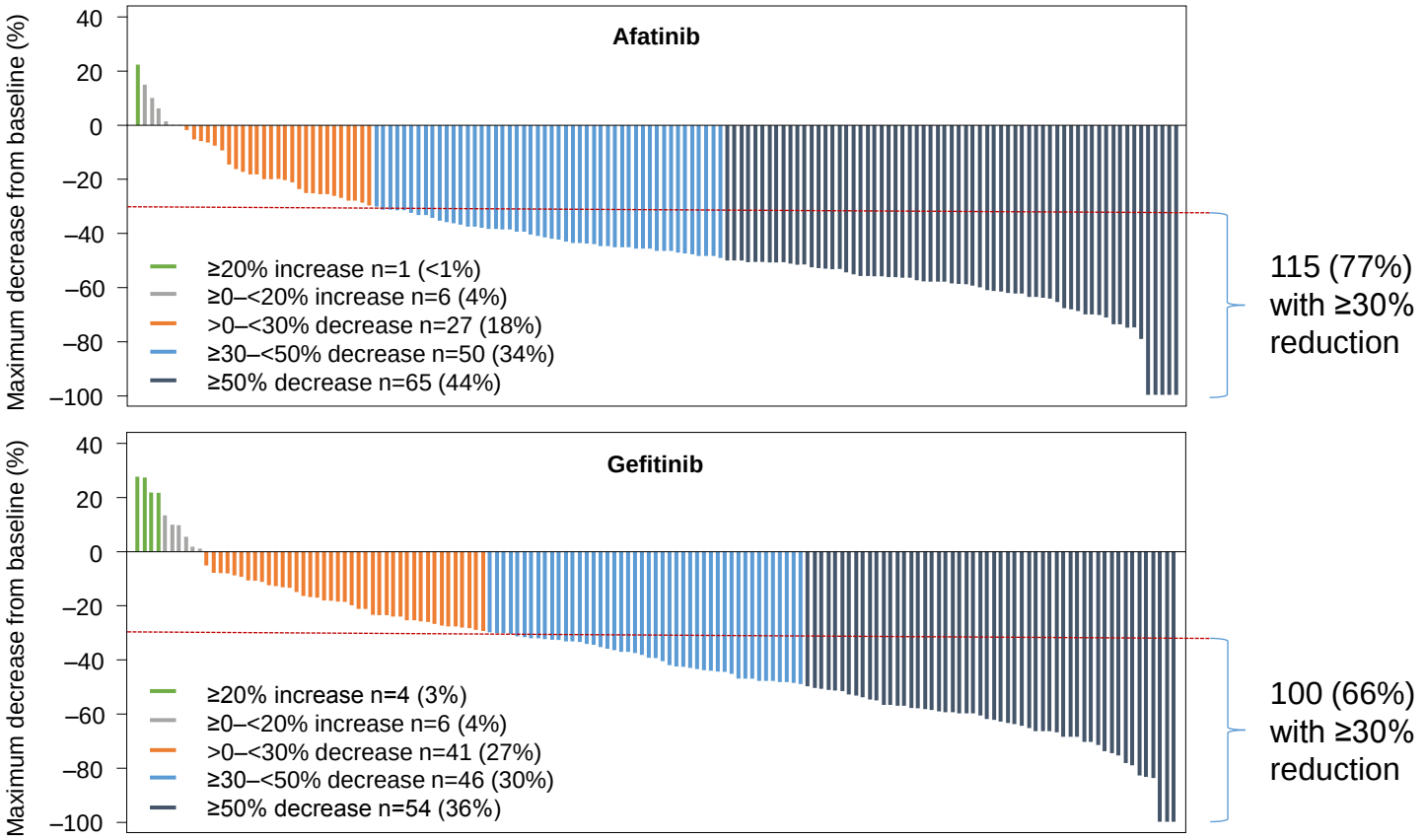
- Afatinib significantly improved PFS of patients with *EGFR*m+ NSCLC relative to gefitinib. Results are consistent across subgroups
- Afatinib treatment was associated with a significant improvement in response rate and TTF
- The improvement in efficacy was observed in both Del19 and L858R populations
- OS data 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

Acknowledgments

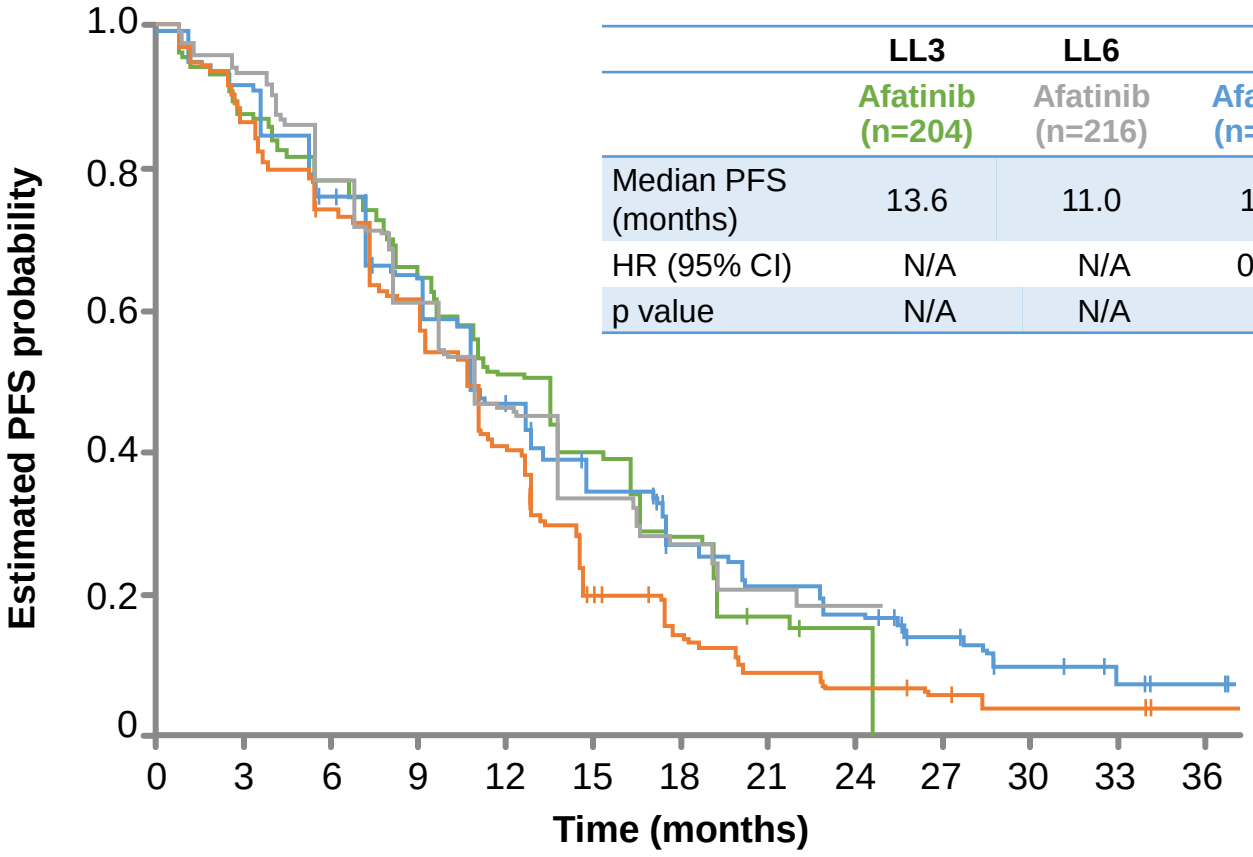
- Thank you to all of the patients and their families, and the LUX-Lung 7 study investigators and their teams for participating in this study

Back-up

Tumor 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	