Dynamic changes in quality of life after three first-line therapies for EGFR mutation-positive advanced non-small cell lung cancer

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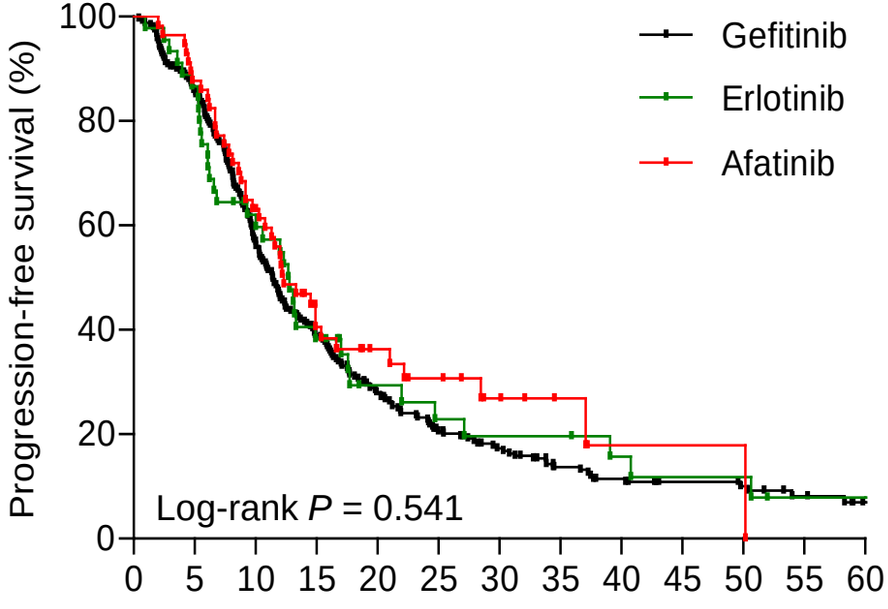
Supplementary Figure 1. Progression-free survival and overall survival stratified according to different first-line treatments.

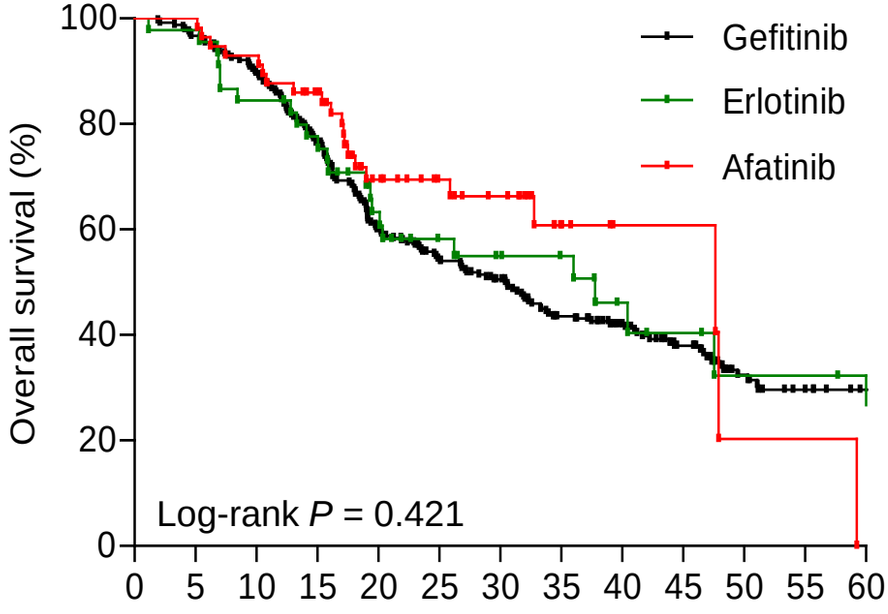
Supplementary Figure 2. Fluctuations in utility values and QoL scores in 4 domains after first-line treatment with erlotinib versus gefitinib. The colored shadow illustrates a 95% confidence interval for each function. QoL: quality of life.

Supplementary Figure 3. Score changes in 9 facets after first-line treatment with erlotinib versus gefitinib. The colored shadow illustrates a 95% confidence interval for each function.

Supplementary Figure 1

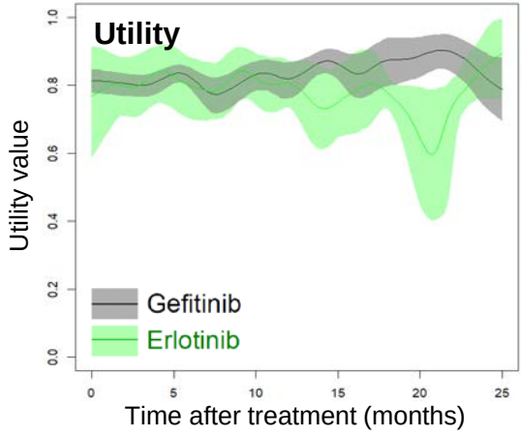


No. of subjects at risk													
Gefitinib	242	209	138	94	66	47	37	25	20	15	13	9	4
Erlotinib	45	40	27	17	10	8	7	7	5	4	4	2	2
Afatinib	57	51	37	21	14	11	7	4	2	2	2	0	0

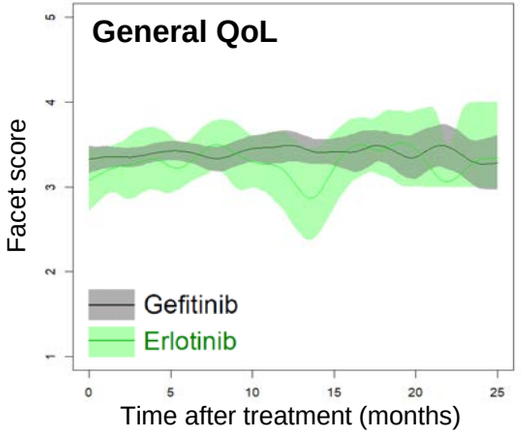


No. of subjects at risk													
Gefitinib	242	235	218	185	144	126	113	92	77	59	36	28	23
Erlotinib	45	45	39	35	26	19	16	14	9	7	5	5	4
Afatinib	57	57	54	46	30	23	19	9	4	4	2	2	0

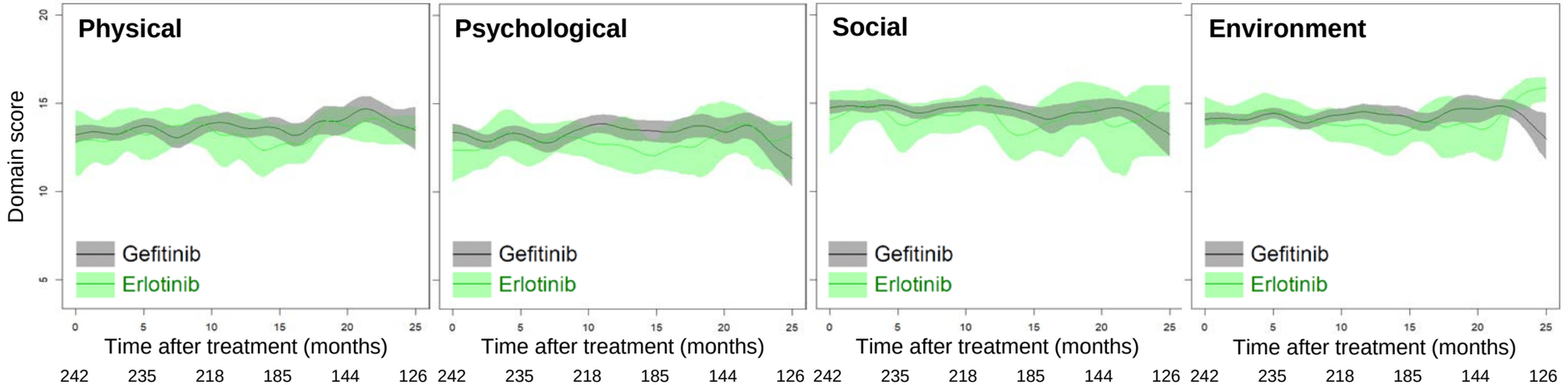
Supplementary Figure 2



Gefitinib						
No. of subjects	242	235	218	185	144	126
No. of QoLs assessed after this time point	662	424	277	185	130	91
Erlotinib						
No. of subjects	45	45	39	35	26	19
No. of QoLs assessed after this time point	119	82	56	35	19	13

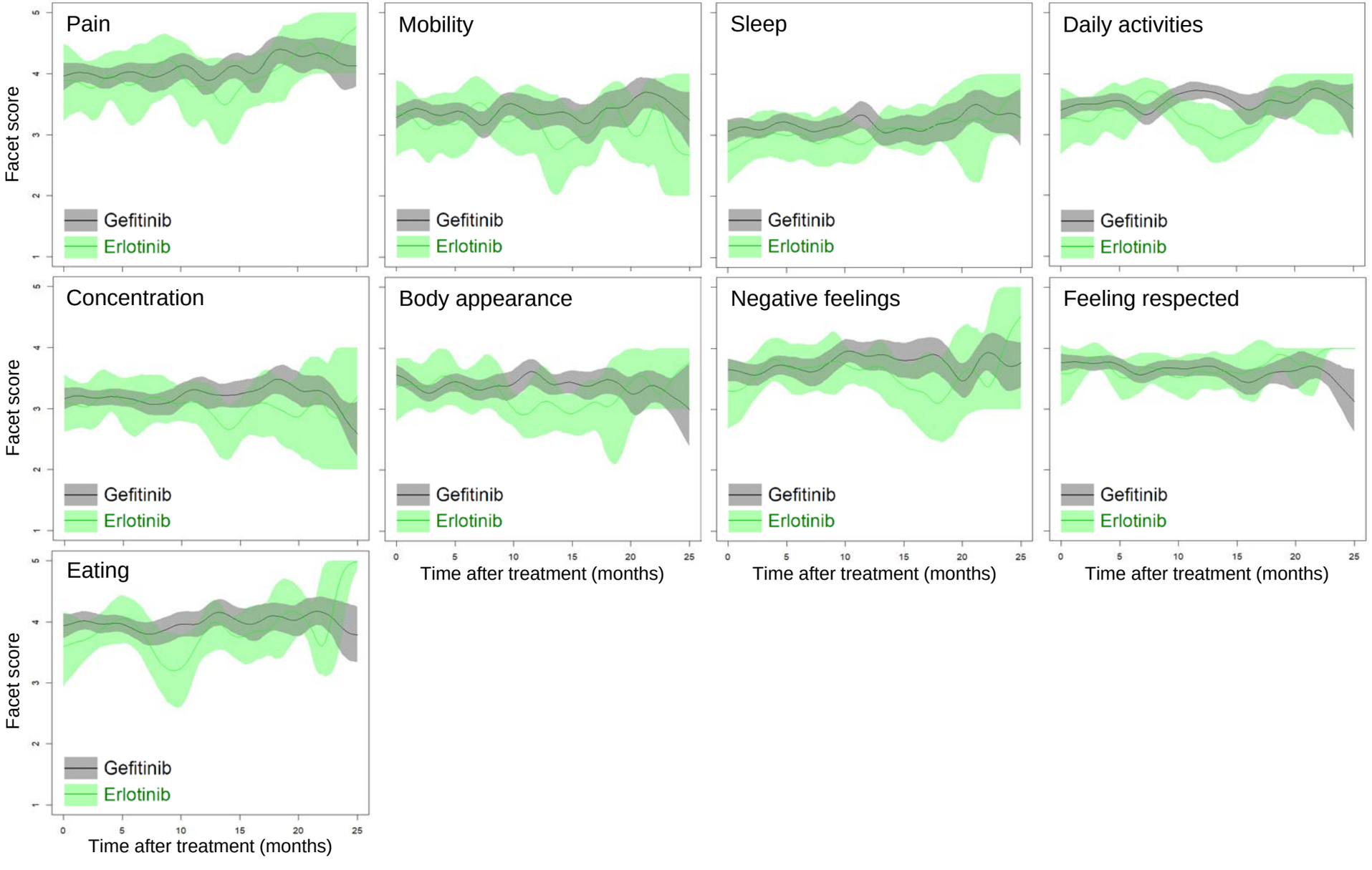


Gefitinib						
No. of subjects	242	235	218	185	144	126
No. of QoLs assessed after this time point	661	422	275	183	129	90
Erlotinib						
No. of subjects	45	45	39	35	26	19
No. of QoLs assessed after this time point	118	80	55	35	19	13



Gefitinib																							
No. of subjects	242	235	218	185	144	126	242	235	218	185	144	126	242	235	218	185	144	126	242	235	218	185	144	126
No. of QoLs assessed after this time point	660	422	275	183	129	90	661	422	275	183	129	90	661	422	275	183	129	90	661	422	275	183	129	90
Erlotinib																								
No. of subjects	45	45	39	35	26	19	45	45	39	35	26	19	45	45	39	35	26	19	45	45	39	35	26	19
No. of QoLs assessed after this time point	118	80	55	35	19	13	118	80	55	35	19	13	118	80	55	35	19	13	118	80	55	35	19	13

Supplementary Figure 3



Supplementary Table 1. Frequency distribution of the number of QoL assessments per participant

Number of QoL assessments	Participants, *n (%)*
1	119 (34.6)
2	84 (24.4)
3	69 (20.1)
4	21 (6.1)
5	15 (4.4)
6	12 (3.5)
7	7 (2.0)
8	7 (2.0)
9	2 (0.6)
10	3 (0.9)
11	4 (1.2)
12	1 (0.3)

Supplementary Table 2. Demographic and clinical characteristics of participants with common EGFR mutations

Number of subjects	Gefitinib *n* = 225	Erlotinib *n* = 44	Afatinib *n* = 48	*P*
Number of assessments, *n*	631	120	116	
Age[a], mean (SD) years	63.7 (11.1)	62.0 (12.9)	60.1 (10.1)	0.117[b]
Male, *n* (%)	85 (37.8)	19 (43.2)	20 (41.7)	0.739
Education, *n* (%)				
≥ 12 years	41 (18.2)	15 (34.1)	16 (33.3)	0.012
< 12 years	183 (81.3)	29 (65.9)	32 (66.7)	
Missing	1 (0.4)	0	0	
Employment, *n* (%)				
Employed	51 (22.7)	12 (27.3)	17 (35.4)	0.146
Unemployed	174 (77.3)	32 (72.7)	30 (62.5)	
Missing	0	0	1 (2.1)	
Marital status, *n* (%)				
Married	167 (74.2)	36 (81.8)	39 (81.3)	0.381
Single/divorced/widowed	58 (25.8)	8 (18.2)	9 (18.8)	
Comorbidities, *n* (%)				
Cerebrovascular disease	8 (3.6)	4 (9.1)	1 (2.1)	0.178
Coronary artery disease	11 (4.9)	2 (4.6)	1 (2.1)	0.691
COPD	13 (5.8)	4 (9.1)	2 (4.2)	0.591
Diabetes mellitus	26 (11.6)	6 (13.6)	3 (6.3)	0.476
End-stage renal disease	8 (3.6)	1 (2.3)	1 (2.1)	0.814
Performance status[a], *n* (%)				
ECOG: 0-1	205 (91.1)	38 (86.4)	46 (95.8)	0.267
ECOG: 2-4	19 (8.4)	6 (13.6)	2 (4.2)	
Missing	1 (0.4)	0	0	
Disease by recurrence, *n* (%)				
Recurrent lung cancer	42 (18.7)	9 (20.5)	9 (18.8)	0.962
Newly-diagnosed lung cancer	183 (81.3)	35 (79.6)	39 (81.3)	
Mutation subtype, *n* (%)				
Exon 19 deletions	98 (43.6)	18 (40.9)	30 (62.5)	0.044
L858R substitution	127 (56.4)	26 (59.1)	18 (37.5)	
Brain metastasis[a], *n* (%)	51 (22.7)	22 (50.0)	15 (31.3)	0.001
PFS, median (IQR) months	11.8 (7.7-21.9)	12.8 (6.1-24.7)	12.2 (7.1-28.5)	0.824

[a] At the initiation of treatment. [b] $P = 0.041$ using *t* test to compare afatinib with gefitinib.

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IQR, interquartile range; PFS, progression-free survival; SD, standard deviation.

Supplementary Table 3. Regression coefficients based on mixed model analyses in participants with common EGFR mutations

	Sex (male/female)	Education (≥12/<12)	COPD (no/yes)	ECOG (0-1/2-4)	EGFR (del19/L858R)	Brain metastasis (yes/no)	Disease progression (yes/no)	Erlotinib vs. Gefitinib	Afatinib vs. Gefitinib
EQ-5D:									
Utility value				0.26(0.03)[c]		-0.04(0.02)[a]	-0.08(0.02)[c]		
WHOQOL-BREF:									
General QoL		0.26(0.08)[c]		0.43(0.11)[c]	0.14(0.06)[a]		-0.35(0.08)[c]		-0.25(0.09)[b]
Physical		0.65(0.29)[a]		2.47(0.36)[c]	0.54(0.23)[a]	-0.54(0.26)[a]	-0.73(0.26)[b]		-0.73(0.32)[a]
Pain				0.78(0.15)[c]			-0.33(0.12)[b]		-0.31(0.12)[a]
Energy/fatigue			0.36(0.14)[a]	0.43(0.13)[b]	0.19(0.08)[a]	-0.24(0.09)[b]	-0.34(0.10)[c]		
Mobility				1.27(0.13)[c]	0.18(0.08)[a]	-0.20(0.09)[a]	-0.27(0.10)[b]		
Sleep	0.21(0.10)[a]		0.45(0.16)[b]						-0.26(0.12)[a]
Daily activities				0.91(0.11)[c]	0.21(0.07)[b]	-0.15(0.08)[a]	-0.21(-0.08)[b]		-0.24(0.09)[a]
Psychological	0.63(0.27)[a]	0.63(0.31)[a]		1.83(0.38)[c]	1.02(0.25)[c]		-0.74(0.26)[b]		-1.04(0.35)[b]
Concentration		0.32(0.10)[b]		0.54(0.13)[c]	0.26(0.08)[c]	-0.22(0.09)[a]	-0.29(0.09)[b]		-0.28(0.11)[b]
Body appearance	0.27(0.09)[b]			0.33(0.14)[a]	0.21(0.08)[a]		-0.23(0.10)[a]		-0.38(0.11)[b]
Negative feelings	0.37(0.10)[c]			0.43(0.15)[b]	0.35(0.09)[c]				-0.35(0.13)[b]
Social				0.97(0.32)[b]	0.48(0.21)[a]		-0.42(0.21)[a]		-1.16(0.29)[c]
Feeling respected					0.16(0.07)[a]		-0.17(0.08)[a]		-0.24(0.09)[b]
Environment		0.75(0.23)[b]		1.13(0.28)[c]	0.40(0.19)[a]		-0.50(0.19)[b]		
Financial support		0.59(0.12)[c]							
Leisure activities		0.32(0.12)[b]		0.78(0.16)[c]			-0.30(0.11)[b]		
Eating				0.29(0.14)[a]					-0.25(0.12)[a]

Mixed model analyses adjusted for age, sex, education, employment, marital status, comorbidities, performance status, recurrence, EGFR mutation subtype, brain metastasis, disease progression and treatment. Values in parentheses are standard errors. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; those with $p \geq 0.05$ are left blank.

COPD, chronic obstructive pulmonary disease; del19, exon 19 deletions; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D, EuroQol five-dimension questionnaire; QoL, quality of life; WHOQOL-BREF, World Health Organization Quality-of-Life—Brief version.

Supplementary Table 4. Demographic and clinical characteristics of participants with newly-diagnosed lung cancer

Number of subjects	Gefitinib *n* = 196	Erlotinib *n* = 36	Afatinib *n* = 45	*P*
Number of assessments, *n*	497	71	102	
Age[a], mean (SD) years	63.8 (11.6)	62.4 (12.2)	59.6 (10.0)	0.078[b]
Male, *n* (%)	71 (36.2)	18 (50.0)	18 (40.0)	0.290
Education, *n* (%)				
≥ 12 years	33 (16.8)	12 (33.3)	15 (33.3)	0.011
< 12 years	162 (82.7)	24 (66.7)	30 (66.7)	
Missing	1 (0.5)	0	0	
Employment, *n* (%)				
Employed	39 (19.9)	10 (27.8)	14 (31.1)	0.153
Unemployed	157 (80.1)	26 (72.2)	29 (64.4)	
Missing	0	0	2 (4.4)	
Marital status, *n* (%)				
Married	143 (73.0)	33 (91.7)	34 (75.6)	0.055
Single/divorced/widowed	53 (27.0)	3 (8.3)	11 (24.4)	
Comorbidities, *n* (%)				
Cerebrovascular disease	7 (3.6)	2 (5.6)	0	0.335
Coronary artery disease	10 (5.1)	1 (2.8)	1 (2.2)	0.615
COPD	11 (5.6)	3 (8.3)	2 (4.4)	0.745
Diabetes mellitus	23 (11.7)	6 (16.7)	1 (2.2)	0.087
End-stage renal disease	9 (4.6)	1 (2.8)	0	0.317
Performance status[a], *n* (%)				
ECOG: 0-1	176 (89.8)	32 (88.9)	40 (88.9)	0.943
ECOG: 2-4	19 (9.7)	4 (11.1)	5 (11.1)	
Missing	1 (0.5)	0	0	
Mutation subtype, *n* (%)				
Exon 19 deletions	81 (41.3)	13 (36.1)	23 (51.1)	0.112
L858R substitution	102 (52.0)	22 (61.1)	16 (35.6)	
Other mutations	13 (6.6)	1 (2.8)	6 (13.3)	
Brain metastasis[a], *n* (%)	52 (26.5)	17 (47.2)	17 (37.8)	0.027
PFS, median (IQR) months	10.8 (6.9-19.4)	12.0 (5.4-17.6)	11.6 (7.4-16.6)	0.862

[a] At the initiation of treatment. [b] $P = 0.024$ using *t* test to compare afatinib with gefitinib.

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PFS, progression-free survival; SD, standard deviation.

Supplementary Table 5. Regression coefficients based on mixed model analyses in participants with newly-diagnosed lung cancer

	Sex (male/female)	Education (≥12/<12)	COPD (no/yes)	ECOG (0-1/2-4)	EGFR (del19+/del19-)	Brain metastasis (yes/no)	Disease progression (yes/no)	Erlotinib vs. Gefitinib	Afatinib vs. Gefitinib
EQ-5D:									
Utility value				0.28(0.03)[c]			-0.07(0.02)[c]		
WHOQOL-BREF:									
General QoL		0.31(0.09)[c]		0.46(0.11)[c]	0.16(0.07)[a]		-0.34(0.09)[c]		-0.34(0.09)[c]
Physical		0.74(0.33)[a]		2.67(0.39)[c]			-0.66(0.30)[a]		
Pain				0.81(0.16)[c]					
Energy/fatigue		0.24(0.12)[a]	0.45(0.17)[b]	0.45(0.14)[b]		-0.21(0.10)[a]	-0.25(0.11)[a]		
Mobility				1.33(0.14)[c]					
Sleep		0.29(0.13)[a]	0.42(0.17)[a]						
Daily activities				0.95(0.12)[c]	0.19(0.08)[a]		-0.24(0.09)[b]		
Psychological		0.94(0.36)[b]		2.03(0.41)[c]	1.00(0.27)[c]		-0.79(0.29)[b]		-0.90(0.37)[a]
Concentration		0.32(0.11)[b]		0.61(0.14)[c]	0.24(0.09)[b]		-0.27(0.11)[a]		
Body appearance	0.24(0.10)[a]			0.32(0.14)[a]			-0.23(0.11)[a]		-0.33(0.12)[b]
Negative feelings	0.28(0.11)[b]			0.46(0.16)[b]	0.36(0.10)[c]				
Social	-0.58(0.24)[a]		0.84(0.41)[a]	1.14(0.34)[c]			-0.56(0.24)[a]		-1.13(0.31)[c]
Feeling respected	-0.17(0.08)[a]				0.17(0.07)[a]		-0.22(0.09)[a]		-0.27(0.10)[b]
Environment		0.90(0.27)[c]		1.30(0.30)[c]			-0.54(0.22)[a]		
Financial support		0.64(0.14)[c]							
Leisure activities	-0.25(0.11)[a]	0.39(0.14)[b]		0.89(0.16)[c]					
Eating				0.45(0.15)[b]					-0.33(0.13)[b]

Mixed model analyses adjusted for age, sex, education, employment, marital status, comorbidities, performance status, EGFR mutation subtype, brain metastasis, disease progression and treatment. Values in parentheses are standard errors. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; those with $p \geq 0.05$ are left blank.

COPD, chronic obstructive pulmonary disease; del19, exon 19 deletions; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D, EuroQol five-dimension questionnaire; QoL, quality of life; WHOQOL-BREF, World Health Organization Quality-of-Life—Brief version.