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2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

Clinical Outcomes and Secondary T790M among Different EGFR TKIs for advanced EGFR-mutated NSCLC in the Real World

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Disclosure

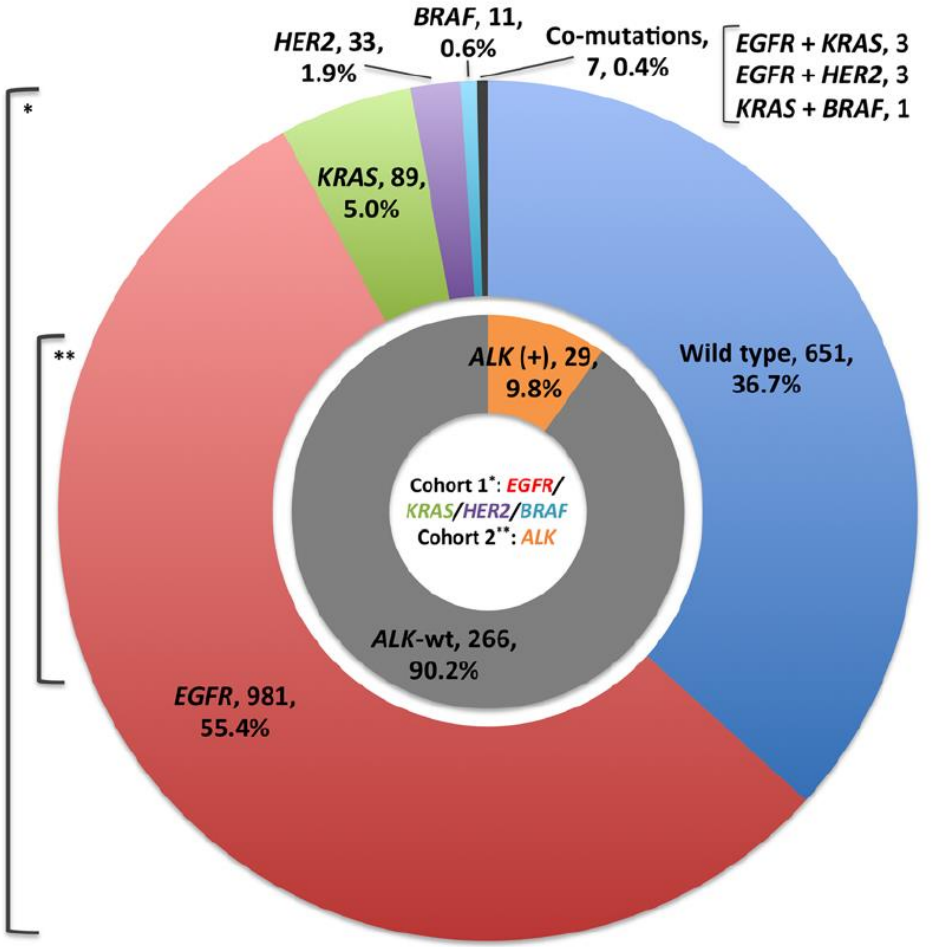
- I received speaking honoraria from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Pfizer, Roche and TTY Biopharm; and travel expense from Pfizer.

Outline

- Introduction
  - Efficacy of First-line EGFR TKIs in RCTs
- Efficacy of EGFR TKIs in the real world
  - Classic EGFR mutations – deletion 19 and L858R
  - Uncommon EGFR mutations
- Secondary T790M in the real world

FDA approved EGFR TKIs

- First generation
  - Gefitinib
  - Erlotinib
- Second generation
  - Afatinib
  - Dacomitinib
- Third generation
  - Osimertinib



Hsu K-H et al. *PLoS ONE. 2015,* 10(3):e0120852. doi:10.1371/journal.pone.0120852

Direct comparison between first-line EGFR TKIs in RCTs

CTONG 0901

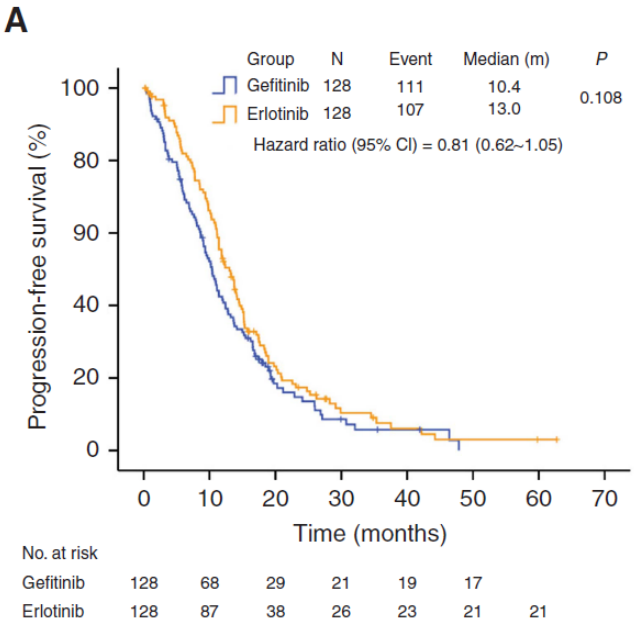
- Erlotinib vs Gefitinib
- RCT
- A single center trial
- N=128/128
- Trial start: 2009/06
- Sponsor: nil

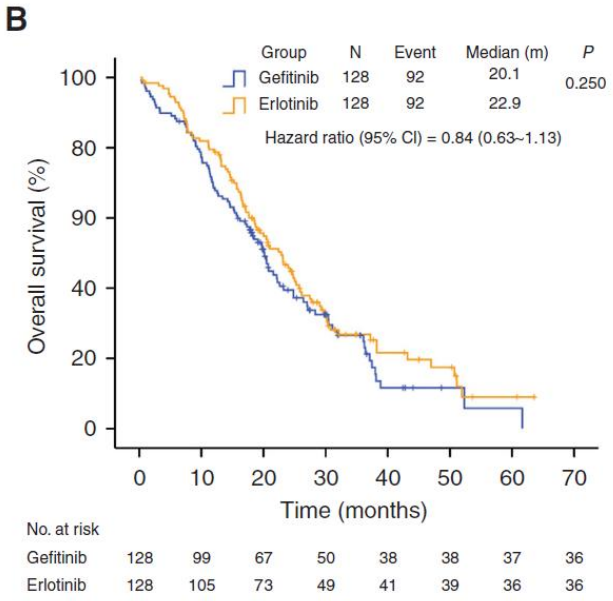
LUX-Lung 7

- Afatinib vs Gefitinib
- RCT
- A global trial
- N=160/159
- Trial start: 2011/12
- Sponsor: Boehringer Ingelheim

CTONG 0901

- Erlotinib
  - Median PFS
    - 13.4 months
  - Median OS
    - 22.9 months
- Gefitinib
  - Median PFS
    - 10.4 months
  - Median OS
    - 20.1 months

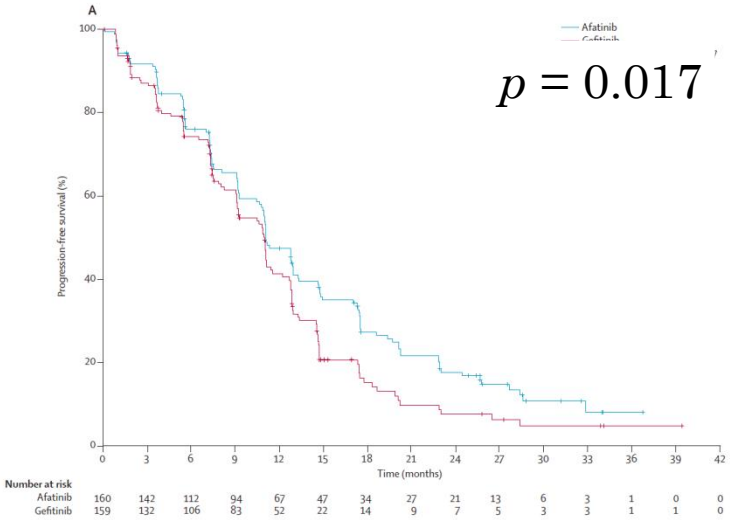


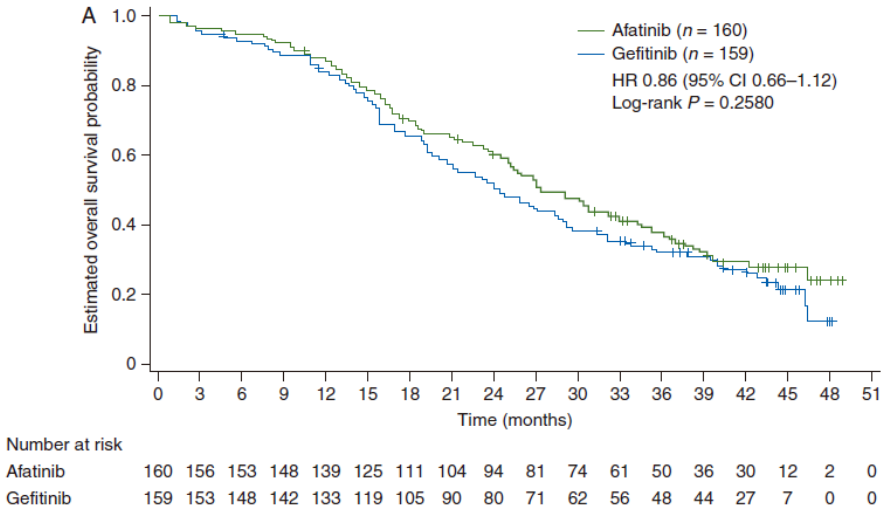


Yang JJ et al. *Br J Cancer*. 2017 Feb 28;116(5):568-574.

LUX-LUNG 7

- Afatinib
  - Median PFS
    - 11.0 months
  - Median OS
    - 27.9 months
- Gefitinib
  - Median PFS
    - 10.9 months (p=0.017)
  - Median OS
    - 24.5 months (p=0.258)

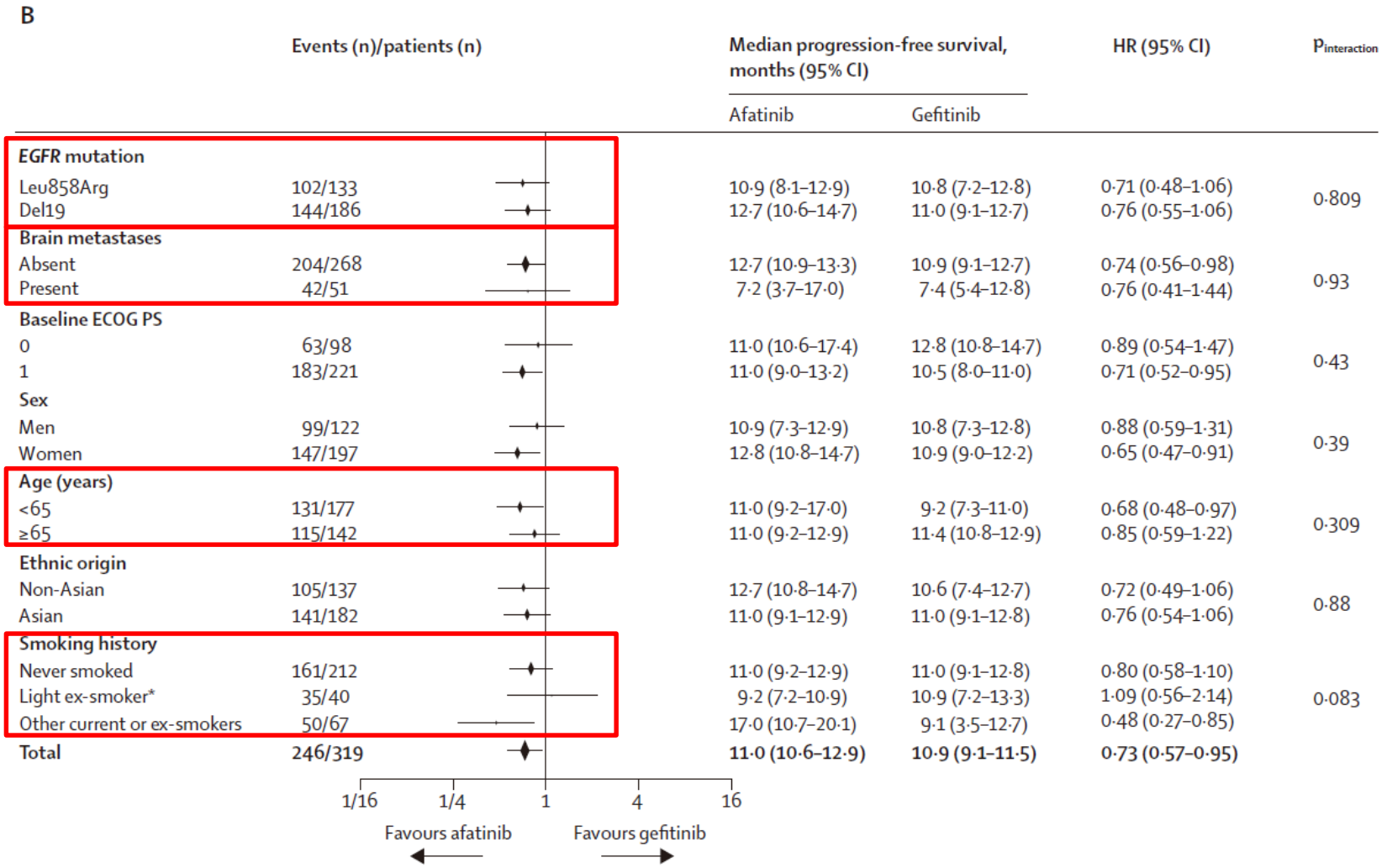




Park K et al. *Lancet Oncol.* 2016; 17: 577–89
Paz-Ares L et al. *Ann Oncol*. 2017 Feb 1;28(2):270-277.

LUX-LUNG 7 PFS

B



	Events (n)/patients (n)	Median progression-free survival, months (95% CI)		HR (95% CI)	$P_{interaction}$
		Afatinib	Gefitinib		
***EGFR* mutation**					
Leu858Arg	102/133	10·9 (8·1–12·9)	10·8 (7·2–12·8)	0·71 (0·48–1·06)	0·809
Del19	144/186	12·7 (10·6–14·7)	11·0 (9·1–12·7)	0·76 (0·55–1·06)	
Brain metastases					
Absent	204/268	12·7 (10·9–13·3)	10·9 (9·1–12·7)	0·74 (0·56–0·98)	0·93
Present	42/51	7·2 (3·7–17·0)	7·4 (5·4–12·8)	0·76 (0·41–1·44)	
Baseline ECOG PS					
0	63/98	11·0 (10·6–17·4)	12·8 (10·8–14·7)	0·89 (0·54–1·47)	0·43
1	183/221	11·0 (9·0–13·2)	10·5 (8·0–11·0)	0·71 (0·52–0·95)	
Sex					
Men	99/122	10·9 (7·3–12·9)	10·8 (7·3–12·8)	0·88 (0·59–1·31)	0·39
Women	147/197	12·8 (10·8–14·7)	10·9 (9·0–12·2)	0·65 (0·47–0·91)	
Age (years)					
<65	131/177	11·0 (9·2–17·0)	9·2 (7·3–11·0)	0·68 (0·48–0·97)	0·309
≥65	115/142	11·0 (9·2–12·9)	11·4 (10·8–12·9)	0·85 (0·59–1·22)	
Ethnic origin					
Non-Asian	105/137	12·7 (10·8–14·7)	10·6 (7·4–12·7)	0·72 (0·49–1·06)	0·88
Asian	141/182	11·0 (9·1–12·9)	11·0 (9·1–12·8)	0·76 (0·54–1·06)	
Smoking history					
Never smoked	161/212	11·0 (9·2–12·9)	11·0 (9·1–12·8)	0·80 (0·58–1·10)	
Light ex-smoker*	35/40	9·2 (7·2–10·9)	10·9 (7·2–13·3)	1·09 (0·56–2·14)	0·083
Other current or ex-smokers	50/67	17·0 (10·7–20·1)	9·1 (3·5–12·7)	0·48 (0·27–0·85)	
Total	**246/319**	**11·0 (10·6–12·9)**	**10·9 (9·1–11·5)**	**0·73 (0·57–0·95)**	

Park K et al. *Lancet Oncol.* 2016; 17: 577–89

LUX-LUNG 7 ADVERSE EFFECTS

	Afatinib (n=160)				Gefitinib (n=159)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Total	106 (66%)	47 (29%)	3 (2%)	0	124 (78%)	26 (16%)	2 (1%)	1 (1%)
Diarrhoea	124 (78%)	19 (12%)	1 (1%)	0	95 (60%)	2 (1%)	0	0
Rash or acne*	127 (79%)	15 (9%)	0	0	124 (78%)	5 (3%)	0	0
Stomatitis†	96 (60%)	7 (4%)	0	0	38 (24%)	0	0	0
Paronychia‡	86 (54%)	3 (2%)	0	0	26 (16%)	1 (1%)	0	0
Dry skin	52 (33%)	0	0	0	59 (37%)	0	0	0
Pruritus	37 (23%)	0	0	0	36 (23%)	0	0	0
Fatigue§	24 (15%)	9 (6%)	0	0	23 (14%)	0	0	0
Decreased appetite	25 (16%)	1 (1%)	0	0	19 (12%)	0	0	0
Nausea	24 (15%)	2 (1%)	0	0	22 (14%)	0	0	0
Alopecia	17 (11%)	0	0	0	24 (15%)	0	0	0
Vomiting	17 (11%)	0	0	0	5 (3%)	1 (1%)	0	0
Increased ALT/AST	16 (10%)	0	0	0	25 (16%)	13 (8%)	1 (1%)	0
Nasal dryness	10 (6%)	1 (1%)	0	0	0	0	0	0
Conjunctivitis¶	7 (4%)	0	0	0	9 (6%)	1 (1%)	0	0
Hand-foot syndrome	5 (3%)	1 (1%)	0	0	3 (2%)	0	0	0
Weight decreased	5 (3%)	1 (1%)	0	0	0	0	0	0
Hypokalaemia	4 (3%)	3 (2%)	0	0	1 (1%)	0	0	0
Neutropenia	2 (1%)	0	1 (1%)	0	1 (1%)	0	0	0
Increased aminotransferases	2 (1%)	0	0	0	0	1 (1%)	0	0
Toxic skin eruption	2 (1%)	1 (1%)	0	0	0	0	0	0
Dehydration	1 (1%)	3 (2%)	0	0	0	0	0	0
Pneumonia	1 (1%)	1 (1%)	0	0	0	0	0	0
Confusional state	1 (1%)	1 (1%)	0	0	0	0	0	0

Efficacy of first-line EGFR TKIs in the RCTs

- The efficacy among first-line gefitinib, erlotinib and afatinib TKI is still controversial.
  - Afatinib has better PFS but more adverse effects.
  - The OS were similar among the 3 EGFR TKIs.

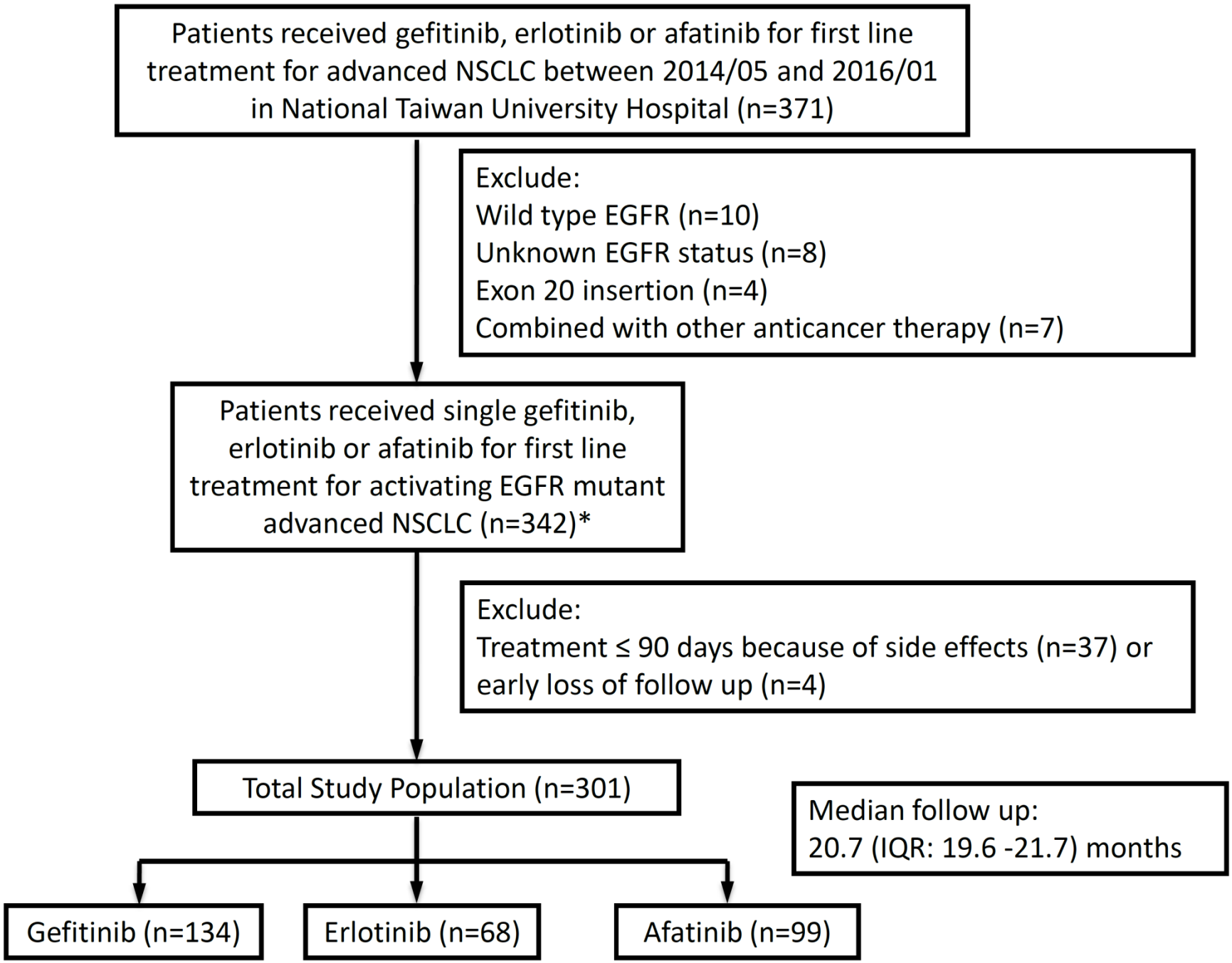

Patients received gefitinib, erlotinib or afatinib for first line treatment for advanced NSCLC between 2014/05 and 2016/01 in National Taiwan University Hospital (n=371)
Exclude:
Wild type EGFR (n=10)
Unknown EGFR status (n=8)
Exon 20 insertion (n=4)
Combined with other anticancer therapy (n=7)
Patients received single gefitinib, erlotinib or afatinib for first line treatment for activating EGFR mutant advanced NSCLC (n=342)*
Exclude:
Treatment ≤ 90 days because of side effects (n=37) or early loss of follow up (n=4)
Total Study Population (n=301)
Median follow up:
20.7 (IQR: 19.6 -21.7) months
Gefitinib (n=134)
Erlotinib (n=68)
Afatinib (n=99)

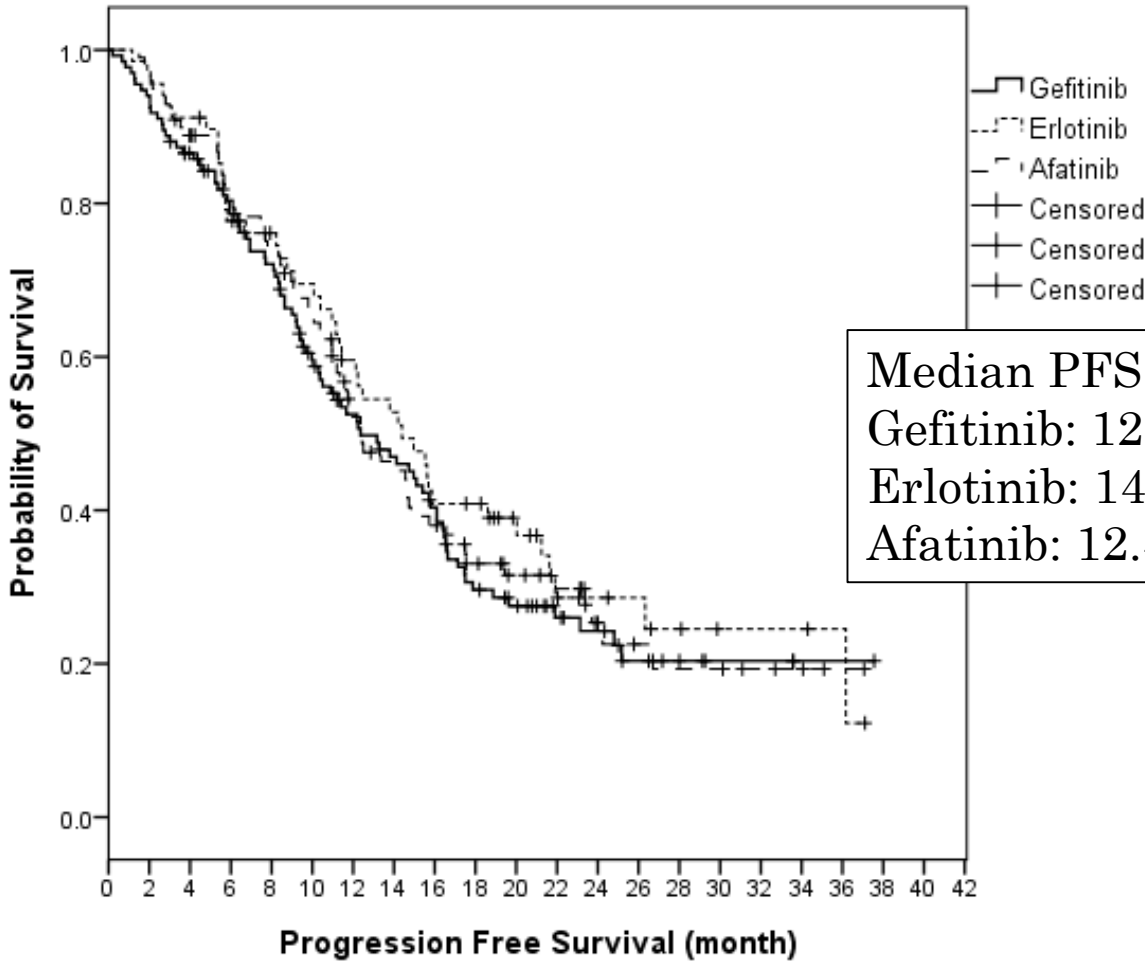
Table 1. Patents' Demographic Data (n = 301)

Variable	Gefitinib (n = 134)	Erlotinib (n = 68)	Afatinib (n = 99)	p
Median age (years old) (IQR)	71 (60–80)	67 (61–73)	60 (53–71)	<0.001 (ANOVA)
Male	36 (27%)	22 (32%)	38 (38%)	0.18
Never smoker	110 (82%)	57 (84%)	66 (67%)	0.007
Adenocarcinoma	130 (97%)	65 (96%)	95 (96%)	0.85
EGFR mutation				<0.001
Del 19	48 (36%)	27 (40%)	59 (60%)	
L858R	76 (57%)	37 (53%)	23 (23%)	
G719X, L861X, S768X	3 (2%)	2 (3%)	13 (13%)	
Single T790M	0 (0%)	0 (0%)	0 (0%)	
Del 19 or L858R or G719X AND T790M	4 (3%)	1 (2%)	2 (2%)	
Other complex	3 (2%)	0 (0%)	2 (2%)	
Others	0 (0%)	1 (2%)	0 (0%)	
Cancer status before EGFR TKI				0.21
Post-operative or post-CCRT recurrence	25 (19%)	17 (25%)	14 (14%)	
Stage IV	109 (81%)	51 (75%)	85 (86%)	
ECOG 0–1 before EGFR TKI	128 (89%)	64 (94%)	92 (93%)	0.26
M1a disease or intrathoracic recurrence only	62 (46%)	16 (24%)	29 (29%)	0.002
Brain metastasis	11 (8%)	38 (56%)	31 (31%)	<0.001
Bone metastasis	45 (34%)	27 (40%)	44 (44%)	0.24
Liver metastasis	13 (10%)	10 (15%)	9 (9%)	0.46
Median follow-up time (month) (IQR)	21.1 (17.4–27.4)	19.5 (12.6–26.6)	20.3 (14.1–25.0)	0.72

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

First line EGFR TKI PFS

n = 301 p = 0.67 by log-rank test

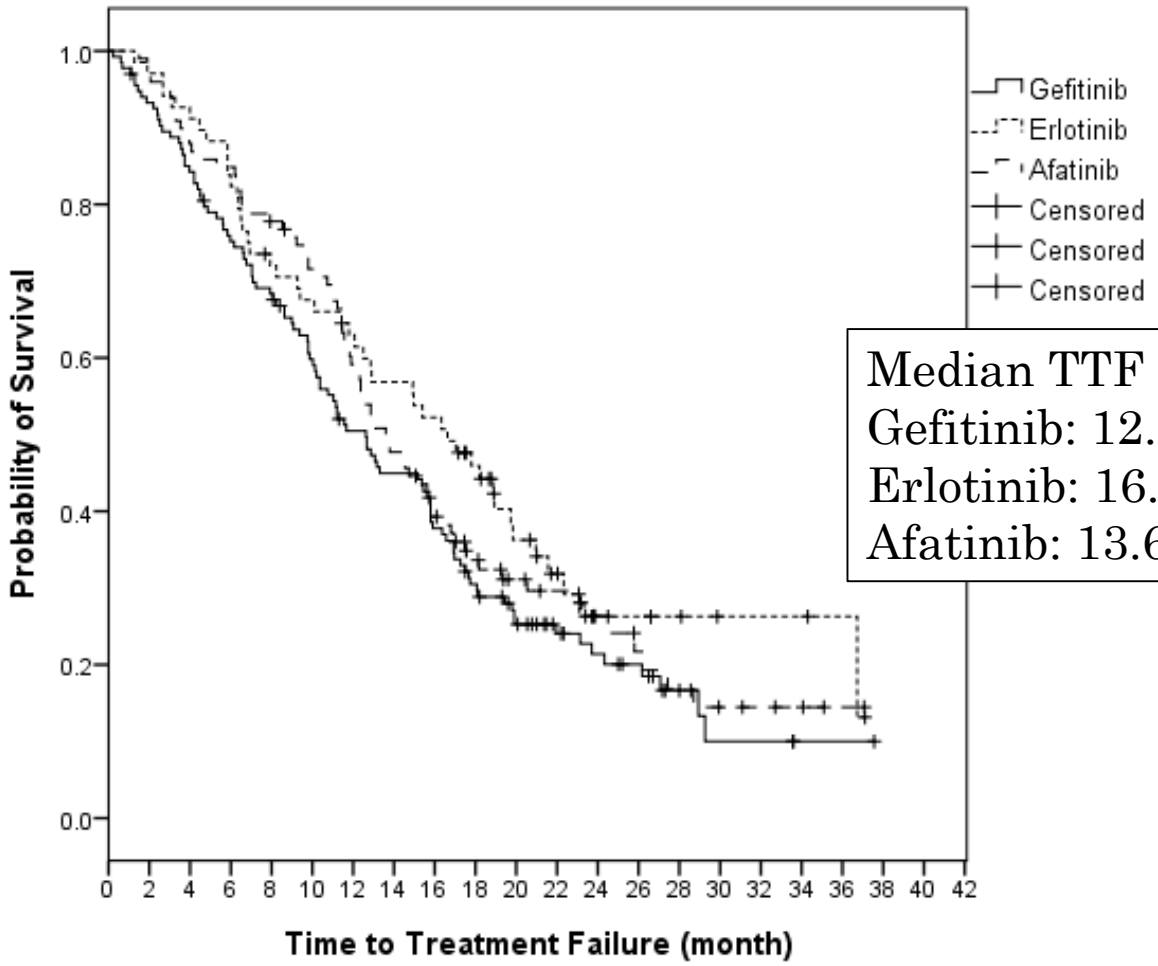


Median PFS (95% CI) (month)
Gefitinib: 12.4 (9.1 – 15.6)
Erlotinib: 14.4 (10.8 – 18.0)
Afatinib: 12.4 (9.8 – 15.0)

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

First line EGFR TKI TTF

n = 301 p = 0.19 by log-rank test



Median TTF (95% CI) (month)
Gefitinib: 12.6 (10.5 – 14.8)
Erlotinib: 16.6 (13.1 – 20.2)
Afatinib: 13.6 (11.7 – 15.5)

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

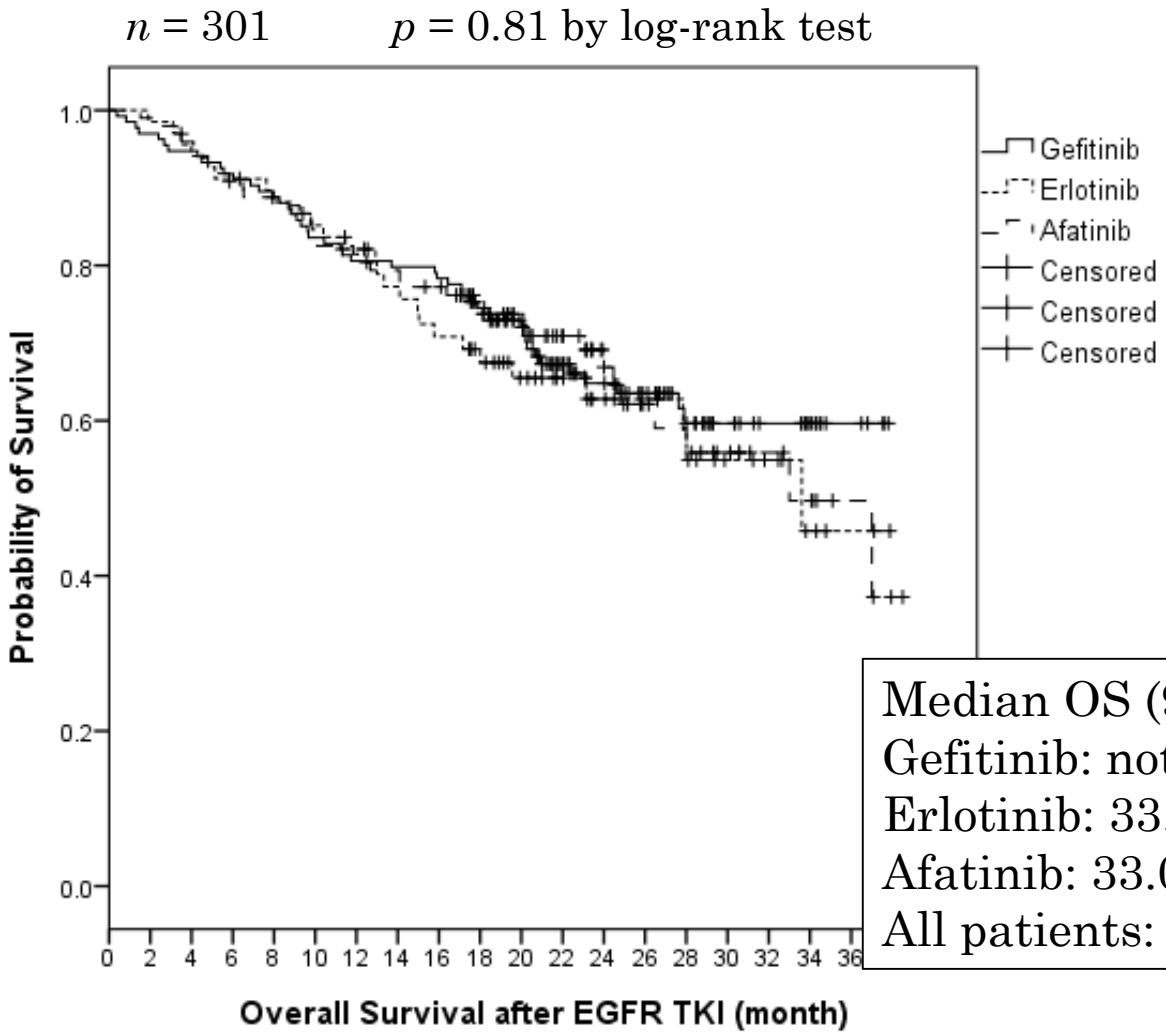
Progression-free Survival

Table 2. Progression-free Survival: Univariate and Multivariate Analysis (n = 301)

	Univariate analysis			Multivariate analysis		
Variable	**Hazard ratio**	**95% CI**	***p* Value**	**Adjusted hazard ratio**	**95% CI**	***p* Value**
Age (≥70)	1.06	0.80–1.41	0.67			
Male sex	1.06	0.79–1.41	0.72			
Never-smoker	0.79	0.58–1.09	0.15			
ECOG ≥2	2.13	1.38–3.30	0.001	1.73	1.09–2.75	0.02
Post-operative recurrence	0.62	0.42–0.91	0.02	0.69	0.46–1.03	0.07
EGFR mutation						
Exon 19 deletion	1.00[2]		0.004	1.00[2]		0.01
L858R	1.20	0.89–1.62	0.23	1.13	0.82–1.56	0.44
Uncommon mutation[1]	2.14	1.37–3.33	0.001	2.02	1.27–3.21	0.003
EGFR TKI						
Gefitinib	1.00[3]		0.67	1.00[3]		0.46
Erlotinib	0.85	0.59–1.22	0.38	0.78	0.52–1.18	0.25
Afatinib	0.94	0.68–1.29	0.68	0.84	0.59–1.21	0.84
M1a or intrathoracic recurrence	0.66	0.48–0.89	0.007	0.82	0.58–1.16	0.27
Initial brain metastasis	1.39	1.02–1.88	0.04	1.27	0.87–1.84	0.21
Initial liver metastasis	1.55	1.03–2.35	0.04	1.45	0.94–2.25	0.09

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

First line EGFR TKI OS



Median OS (95% CI) (month)
Gefitinib: not reached
Erlotinib: 33.6 (not matured)
Afatinib: 33.0 (25.1 – 40.9)
All patients: 37.0 (not matured)

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

Overall Survival

Table 3. Overall survival: univariate and multivariate analysis (n = 301)

	Univariate analysis			Multivariate analysis		
Variable	**Hazard ratio**	**95% CI**	***p* Value**	**Adjusted hazard ratio**	**95% CI**	***p* Value**
Age (≥ 70)	1.31	0.90–1.92	0.16			
Male sex	0.96	0.64–1.43	0.83			
Never-smoker	0.84	0.55–1.30	0.43			
ECOG ≥2	3.11	1.82–5.31	<0.001	2.67	1.52–4.72	0.001
Post-operative recurrence	0.47	0.26–0.84	0.01	0.56	0.31–1.01	0.06
EGFR mutation						
Exon 19 deletion	1.00[2]		0.14	1.00[2]		0.18
L858R	1.10	0.73–1.66	0.65	0.92	0.59–1.42	0.70
Uncommon mutation[1]	1.78	1.00–3.17	0.049	1.61	0.89–2.94	0.12
EGFR TKI						
Gefitinib	1.00[3]		0.81	1.00[3]		0.80
Erlotinib	1.17	0.73–1.90	0.51	0.93	0.54–1.61	0.81
Afatinib	1.07	0.69–1.66	0.77	0.84	0.51–1.39	0.51
M1a or intrathoracic recurrence	0.60	0.39–0.91	0.02	1.00	0.60–1.67	0.99
Initial brain metastasis	2.27	1.54–3.35	<0.001	2.11	1.28–3.46	0.003
Initial liver metastasis	1.63	0.94–2.81	0.08	1.69	0.94–3.03	0.08

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

Conclusions from the study

- In real world practice, choosing first-line EGFR TKI according to patients' clinical characteristics yielded good clinical outcome.
- Neither PFS nor OS difference was seen among gefitinib, erlotinib and afatinib in this real world cohort.
- Uncommon EGFR mutation was associated with shorter PFS while there was no difference between exon 19 deletion and L858R.

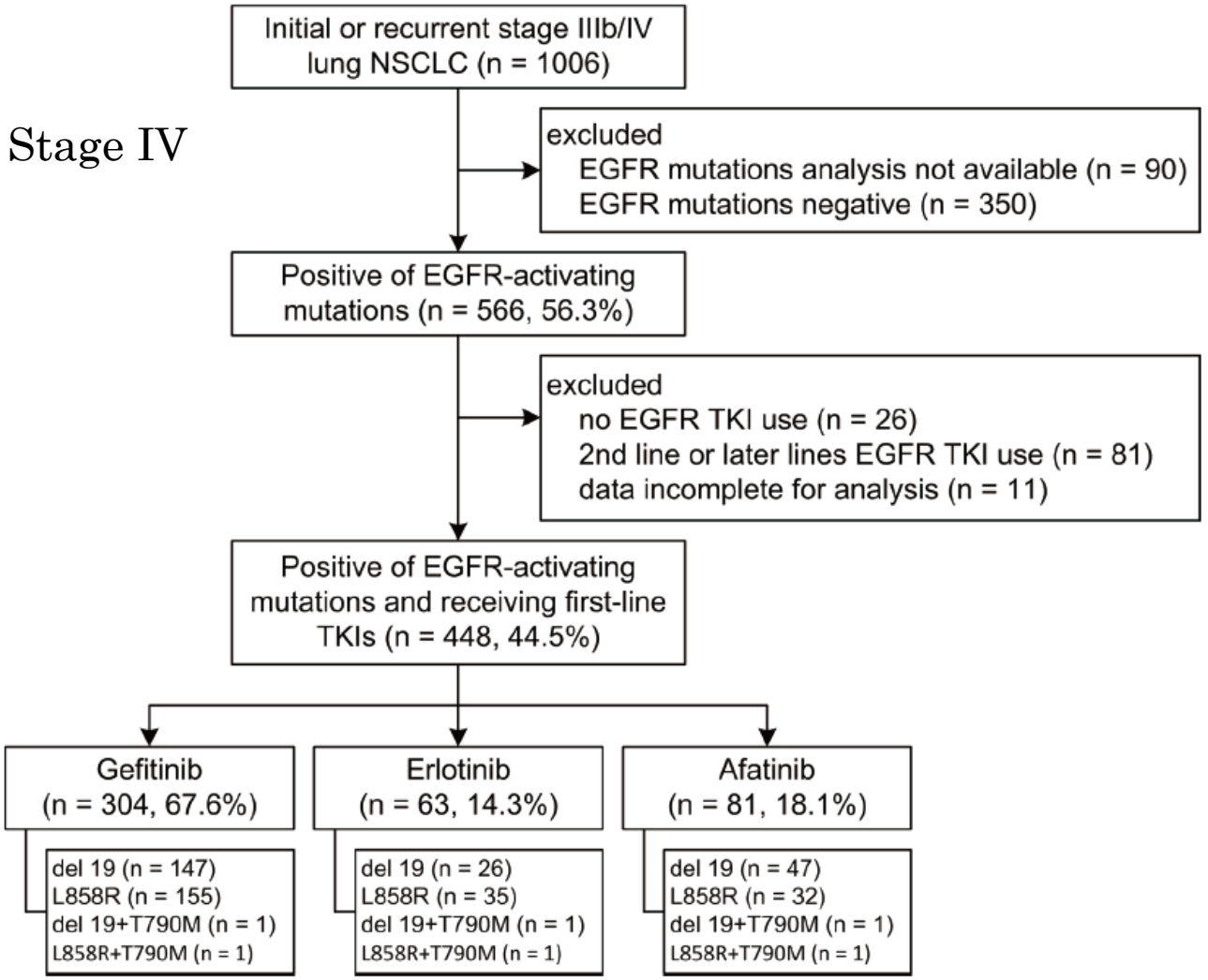
Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

Real-world First-line EGFR TKI efficacy

- Taiwan
  - NTUH cohort — Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.
  - CGMH cohort — Kuan FC et al. *Oncotarget*. 2017 Jan 3;8(1):1343-1353.
  - CMUH cohort — Tu CY et al. *Oncotarget*. 2018 Feb 4;9(36):24237-24247.
- Korea
  - Samsung Medical Center cohort — Kim Y et al. *Cancer Res Treat*. 2019 Apr;51(2):502-509.
  - Asan Medical Center and Koshin University cohort — Yoon BW et al. *Transl Oncol*. 2019 Jun;12(6):852-858.
- Italy
  - MOST study — Pasello G et al. *Oncologist*. 2019 Mar 7. pii: theoncologist.2018-0712. doi: 10.1634/theoncologist.2018-0712.
- US data from administrative claims databases — Lim J et al. *Future Oncol*. 2019 May;15(13):1493-1504.

CGMH COHORT

2011/02/16 -
2015/10/30
Stage IIIB or Stage IV
at CGMH



Kuan FC et al. *Oncotarget*. 2017 Jan 3;8(1):1343-1353.

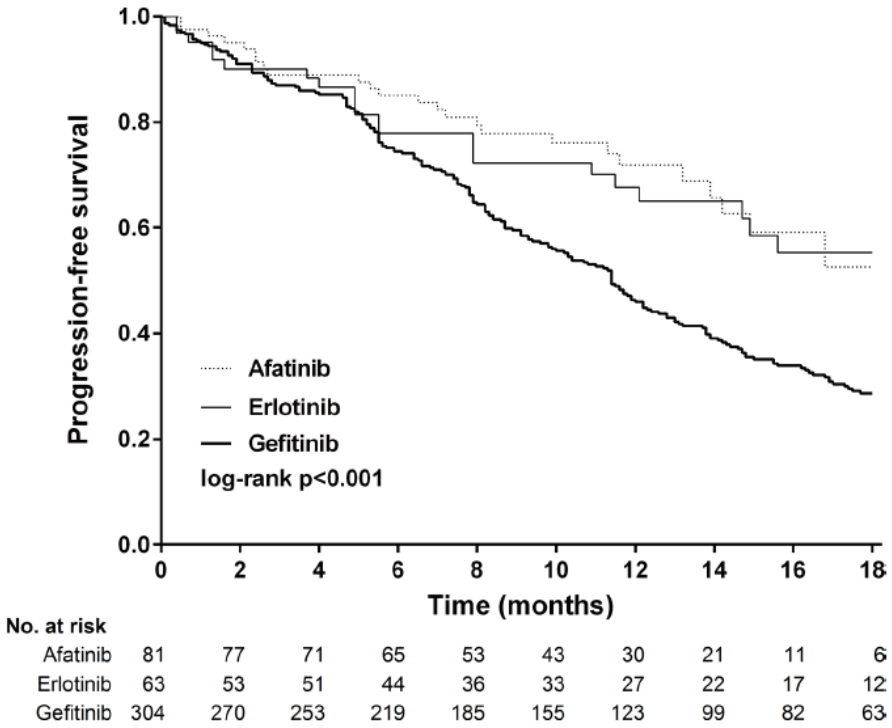
Table 1: Baseline Characteristics for NSCLC by EGFR-TKIs

	EGFR-TKIs						
	Gefitinib		Erlotinib		Afatinib		
	n	(%)	n	(%)	n	(%)	*P*-value
Total	304		63		81		
Sex							0.213
Men	114	(37.5)	24	(38.1)	39	(48.1)	
Women	190	(62.5)	39	(61.9)	42	(51.9)	
Age (years)							0.095
< 65	154	(50.7)	34	(54.0)	52	(64.2)	
≥ 65	150	(49.3)	29	(46.0)	29	(35.8)	
Mean (range)	65	(33–93)	67	(47–90)	64	(37–83)	0.191
Smoking							0.802
Never	226	(74.3)	48	(76.2)	63	(77.8)	
Current or ever	78	(25.7)	15	(23.8)	18	(22.2)	
Clinical stage							0.449
IIIb	16	(5.3)	5	(7.9)	7	(8.6)	
IV	288	(94.7)	58	(92.1)	74	(91.4)	
EGFR mutation							0.119
Del19	148	(48.7)	27	(42.9)	48	(59.3)	
L858R	156	(51.3)	36	(57.1)	33	(40.7)	
Baseline brain metastases							0.867
Absence	244	(80.3)	52	(82.5)	64	(79.0)	
Presence	60	(19.7)	11	(17.5)	17	(21.0)	
ECOG PS							0.017
0 & 1	231	(76.0)	56	(88.9)	70	(86.4)	
> 1	73	(24.0)	7	(11.1)	11	(13.6)	
Grade							0.139
1	59	(19.4)	12	(19.4)	25	(30.9)	
2	64	(21.1)	19	(30.2)	21	(25.9)	
3	49	(16.1)	9	(14.3)	9	(11.1)	
missing	132	(43.4)	23	(36.5)	26	(32.1)	

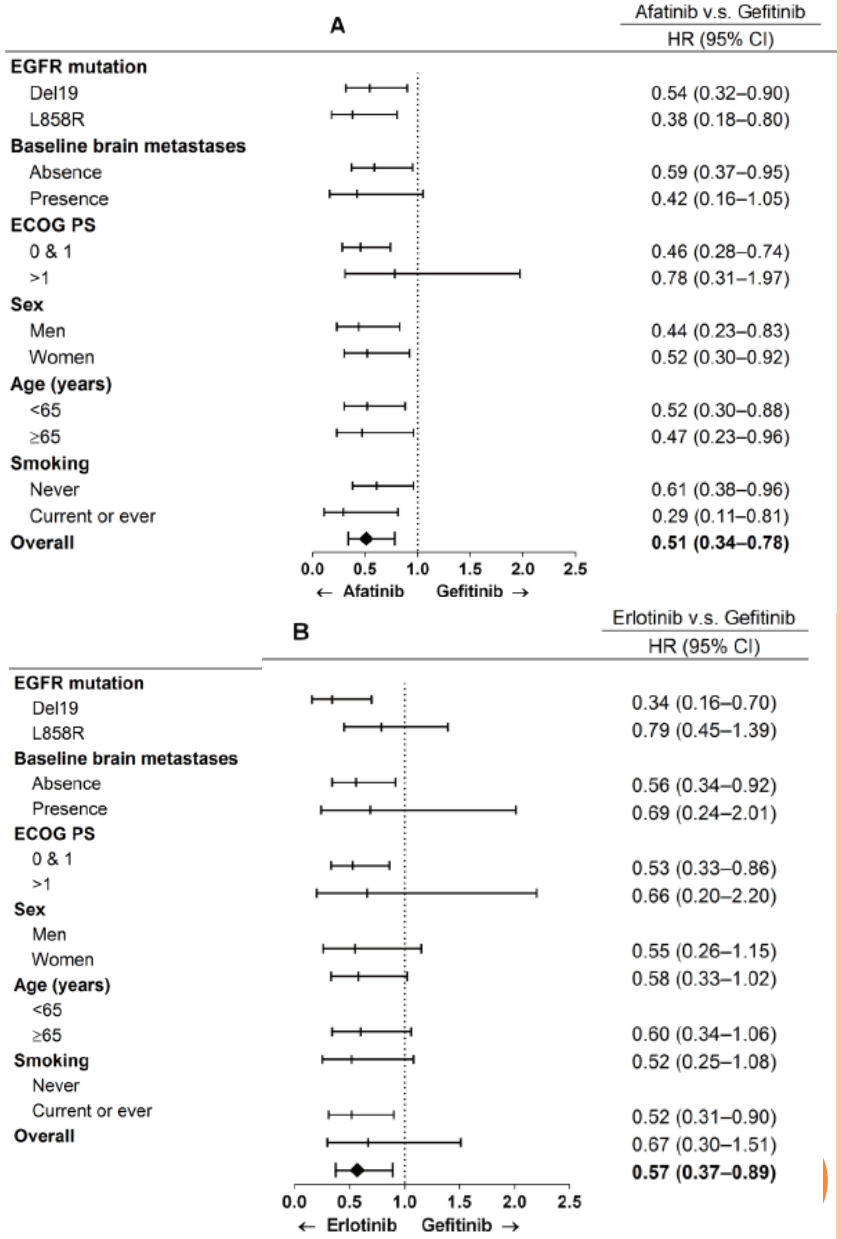
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

Uncommon mutation: Gefitinib: 24 (7.9%); Erlotinib: 5 (7.9%); Afatinib 5 (6.2%)

Kuan FC et al. *Oncotarget*. 2017 Jan 3;8(1):1343-1353.



Median PFS (95% CI) (month)
Gefitinib: 11.4 (9.1 – 15.6)
Erlotinib: not reached
Afatinib: not reached

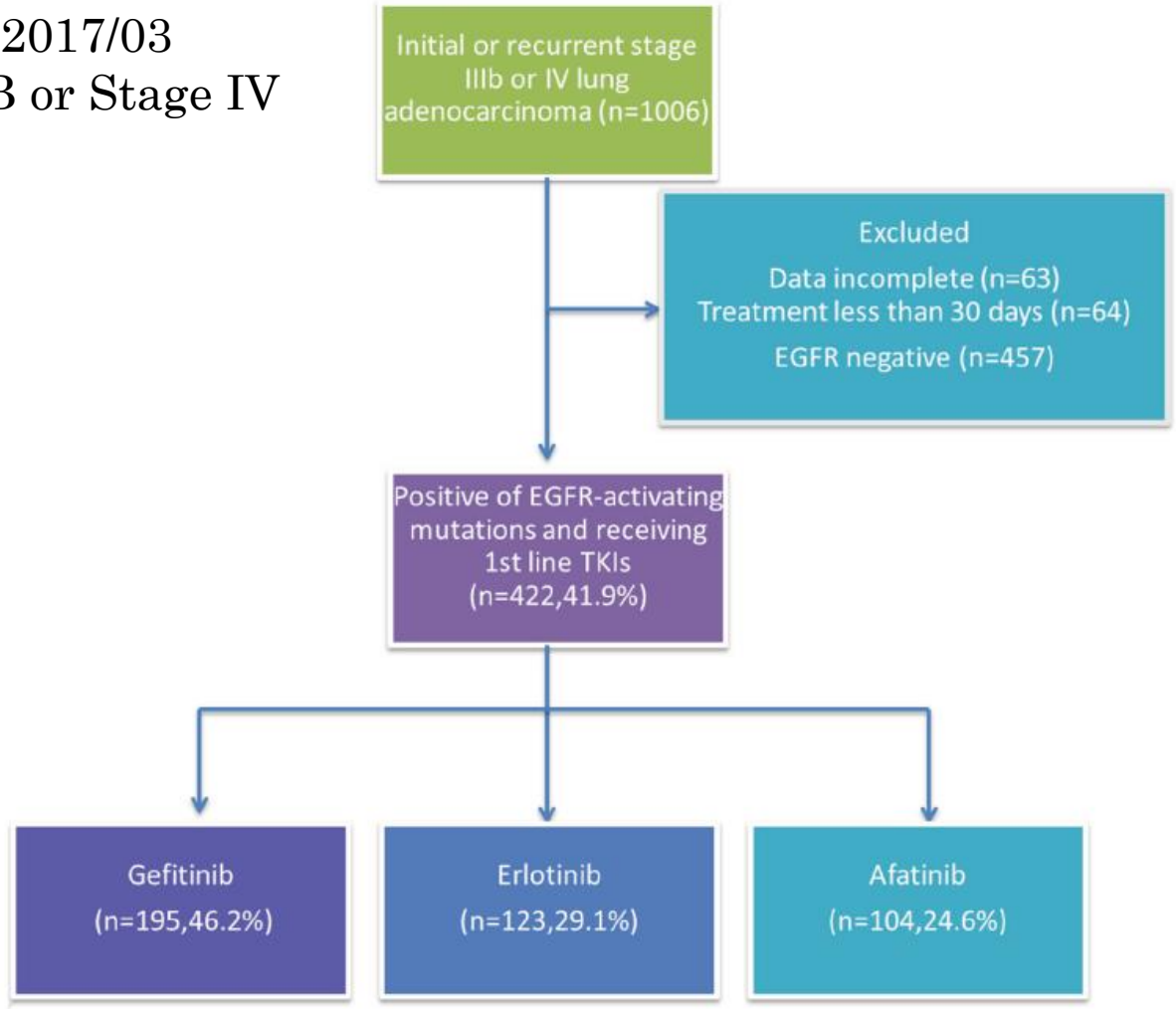


"Very long" erlotinib/afatinib PFS

Kuan FC et al. *Oncotarget*. 2017 Jan 3;8(1):1343-1353.

CMUH COHORT

2013/01 - 2017/03
Stage IIIB or Stage IV
at CMUH



Tu CY et al. *Oncotarget*. 2018 Feb 4;9(36):24237-24247.

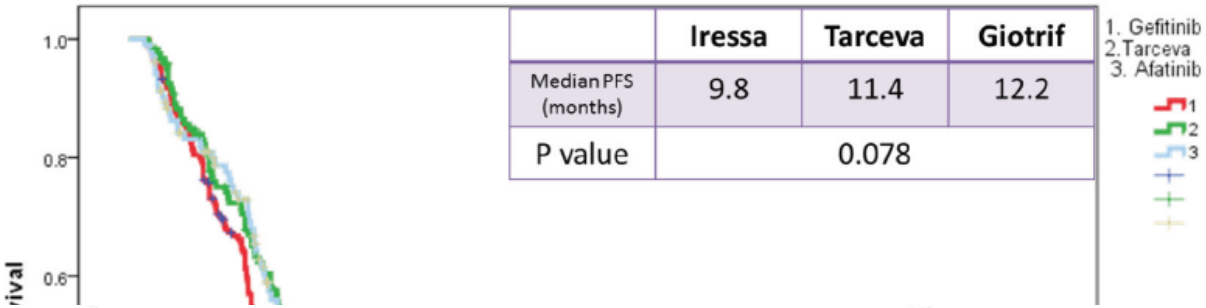
CMUH COHORT

Table 1: Baseline characteristics of NSCLC patients according to EGFR-TKIs

	Gefitinib	Erlotinib	Afatinib	*P* value
	N = 195	*N* = 123	*N* = 104	
Sex				
Men	59 (30.3)	54 (43.9)	39 (37.5)	0.043
Women	136 (69.7)	69 (56.1)	65 (62.5)	
Age (years)				
<65	84 (43.1)	68 (55.3)	58 (55.8)	0.044
>65	111 (56.9)	55 (44.7)	46 (44.2)	
Smoking				
Never	147 (75.4)	92 (74.8)	86 (82.7)	0.446
Current or ever	48 (24.6)	31 (25.2)	18 (17.3)	
BMI				
<20	27 (13.8)	21 (17.1)	17 (16.3)	0.713
>20	168 (86.2)	102 (82.9)	87 (83.7)	
EGFR mutation				
Del19	87 (44.6)	48 (39)	58 (55.8)	0.058
L858R	94 (48.2)	63 (51.2)	23 (22.1)	
Clinical stage				
IIIb	9 (4.6)	3 (2.4)	3 (2.9)	0.543
IV	186 (95.4)	120 (97.6)	101 (97.1)	
ECOG PS				
0 & 1	164 (84.1)	109 (88.6)	93 (89.4)	0.332
> 1	31 (15.9)	14 (11.4)	11 (10.6)	
Baseline brain metastasis				
Absence	161 (82.6)	105 (86.1)	82 (78.8)	0.360
Presence	34 (17.4)	17 (13.9)	22 (21.2)	

Tu CY et al. *Oncotarget*. 2018 Feb 4;9(36):24237-24247.

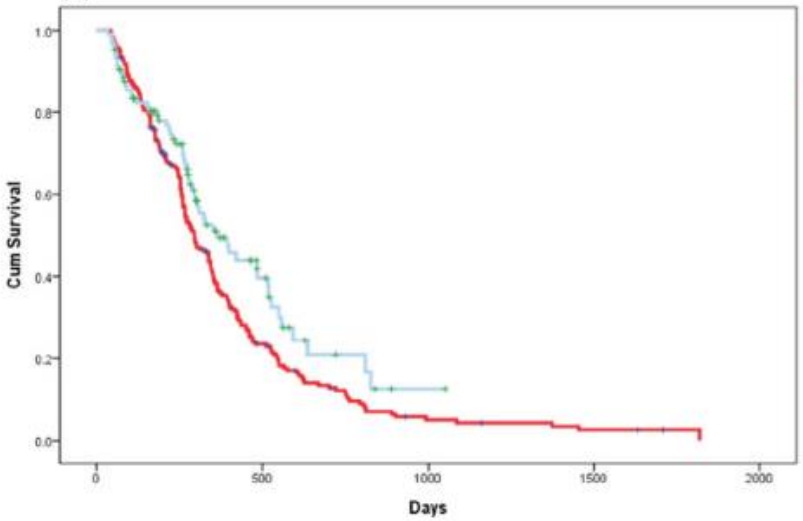
CMUH COHORT



	Iressa	Tarceva	Giotrif
Median PFS (months)	9.8	11.4	12.2
P value	0.078		

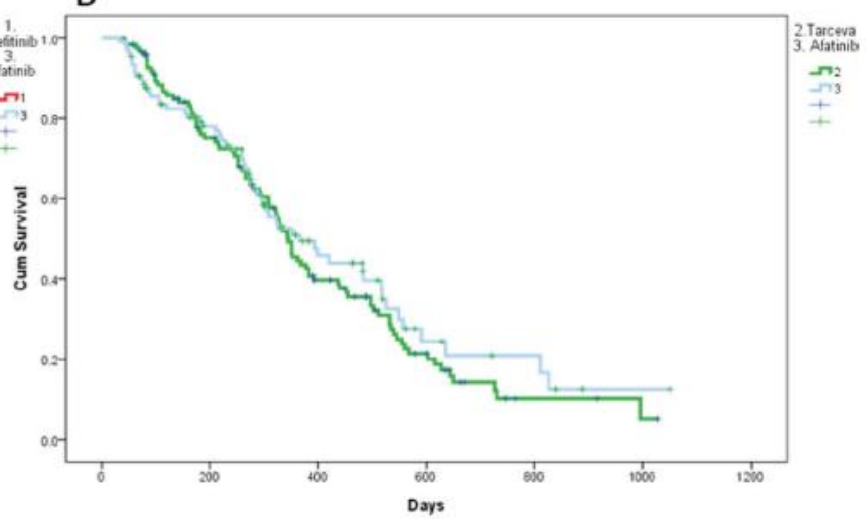
More afatinib in younger and deletion 19 patients.

A



$p = 0.035$

B



$p = 0.38$

Tu CY et al. *Oncotarget*. 2018 Feb 4;9(36):24237-24247.

SAMSUNG MEDICAL CENTER COHORT

2014/10 - 2016/12
Patients received first-line EGFR TKI at Samsung Medical Center

Table 1. Baseline characteristics

Patient characteristic	Afatinib	Gefitinib	Erlotinib	p-value
No. of patients	165	230	72	
Age (yr)				
Median (range)	57 (30-79)	64 (29-87)	59 (36-77)	< 0.001
< 60	93 (56.4)	79 (34.3)	38 (52.8)	< 0.001
≥ 60	72 (43.6)	151(65.7)	34 (47.2)	
Sex				
Male	85 (51.5)	60 (26.1)	39 (54.2)	< 0.001
Female	80 (48.5)	170 (73.9)	33 (45.8)	
ECOG PS				
0	42 (25.5)	56 (24.3)	24 (33.3)	0.658
1	114 (69.0)	160 (69.6)	44 (61.1)	
2	9 (5.5)	14 (6.1)	4 (5.6)	
Smoking status				
Never smoker	99 (60.0)	180 (78.3)	41 (56.9)	< 0.001
Current or ex-smoker	66 (40.0)	50 (21.7)	31 (43.1)	
EGFR mutation type				
Exon 19 deletion	114 (69.1)	122 (53.0)	40 (55.6)	0.002
Exon 21 L858R	37 (22.4)	96 (41.8)	27 (37.5)	
Uncommon EGFR	14 (8.5)	12 (5.2)	5 (6.9)	

Values are presented as median (range) or number (%). Uncommon EGFR: the tumor contains a mutation other than del19 or L858R. ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor.

Lack of cancer stage or brain metastases information

Kim Y et al. *Cancer Res Treat*. 2019 Apr;51(2):502-509.

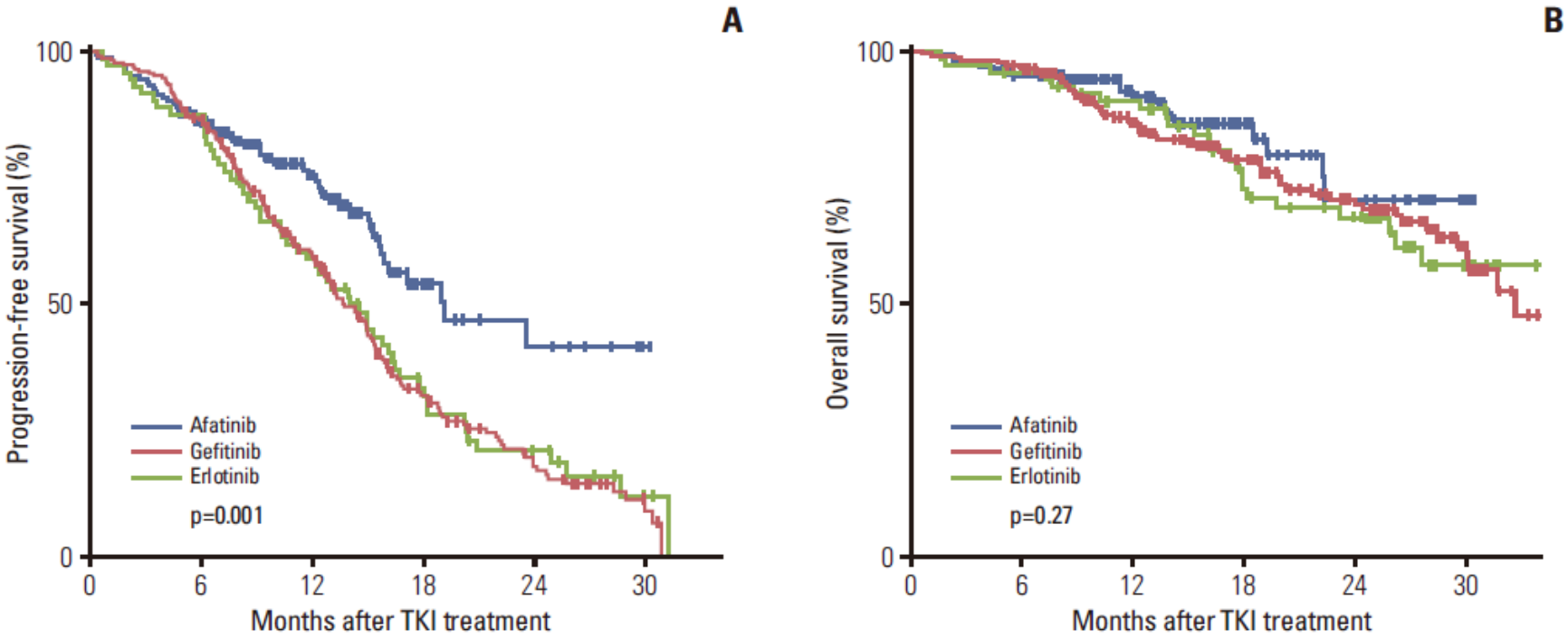


Fig. 1. Progression-free survival (A) and overall survival (B) with afatinib, gefitinib, and erlotinib. TKI, tyrosine kinase inhibitor.

Median PFS (95% CI) (month)
Gefitinib: 13.7 (12.3 – 15.1)
Erlotinib: 14.0 (11.3 – 16.8)
Afatinib: 19.1 (12.3 – 25.9)

Kim Y et al. *Cancer Res Treat*. 2019 Apr;51(2):502-509.

- Univariate analysis for PFS
  - Common EGFR mutation type ($p < 0.001$)
  - Good performance status (Eastern Cooperative Oncology Group 0 or 1) ($p < 0.001$)
  - Never smoker ($p=0.014$)
  - Younger age (< 60 years) ($p=0.174$)
  - Female sex ($p=0.523$)

- Multivariate analysis for PFS
  - Afatinib therapy was significantly associated with longer PFS in the multivariate analysis (HR, 0.46; 95% CI, 0.34 to 0.63; $p < 0.001$).

Kim Y et al. *Cancer Res Treat*. 2019 Apr;51(2):502-509.

Asan Medical Center and Koshin University cohort

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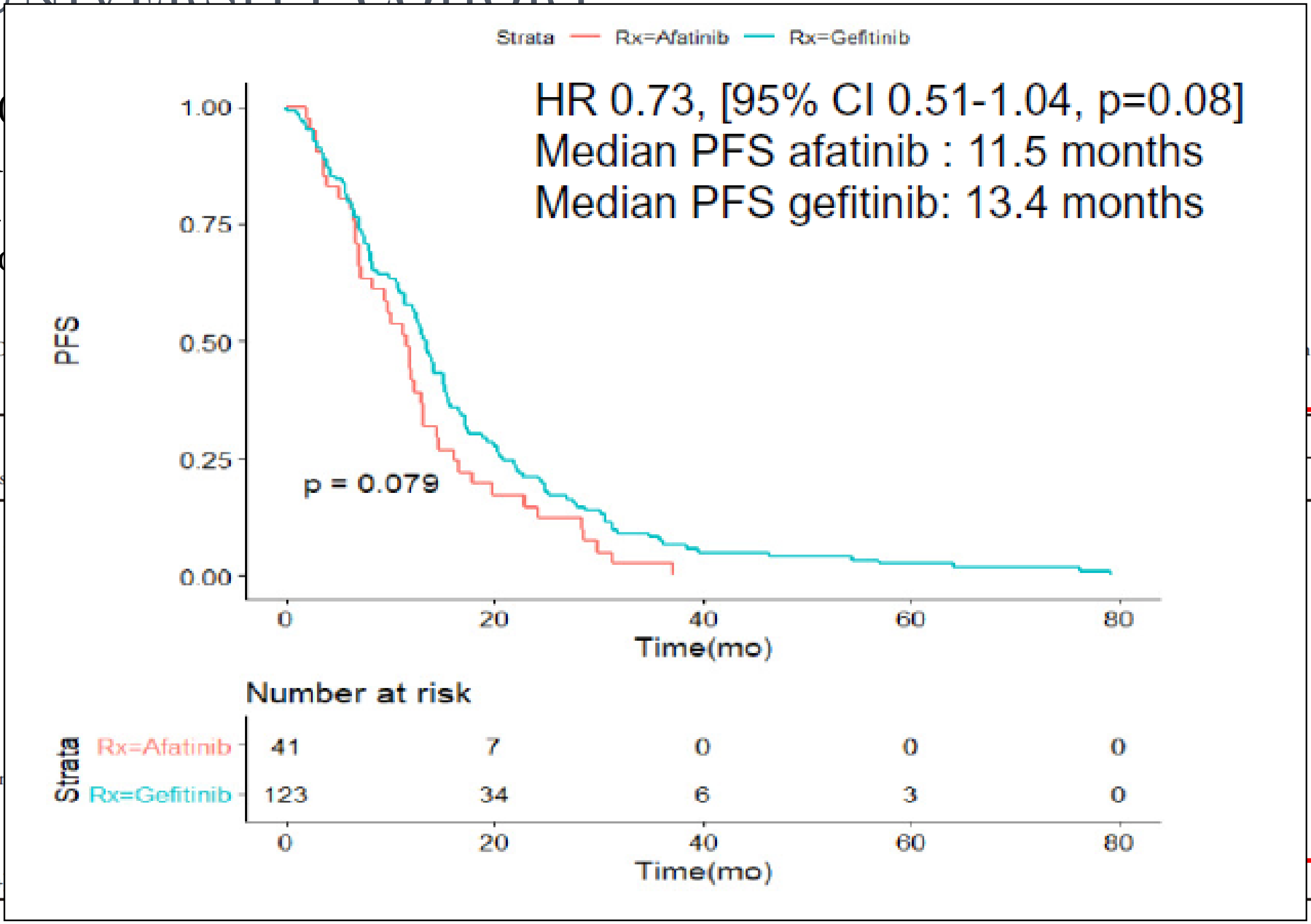
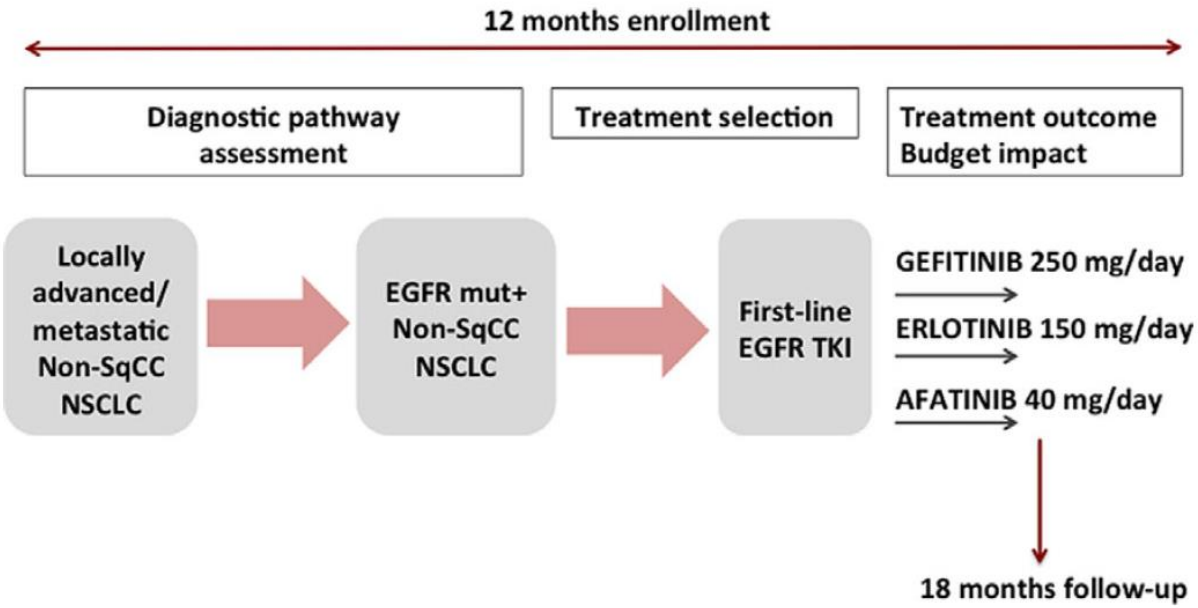
Table 1. C ...sity Score–Matched Results



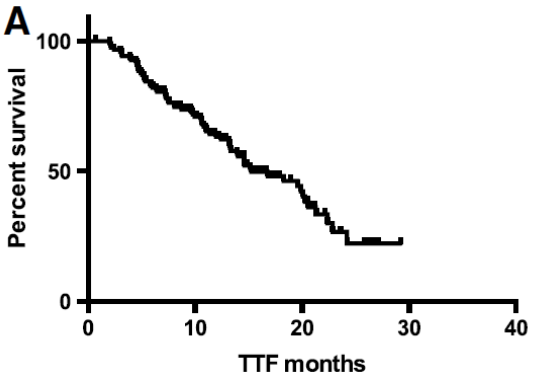
Characteris...	P Value
N	
Age mean	.417
Gender	.928
Male	
Female	
Stage	.992
IIIB	
IVA	
IVB	
1st biopsy	.506
EGFR r...	
E19del	
L858R	
Others	
T790M (+...	.317

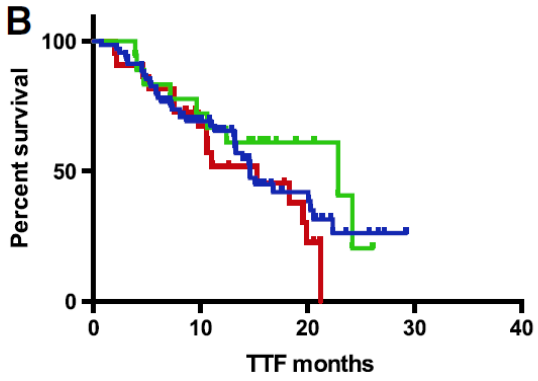
Yoon BW et al. *Transl Oncol*. 2019 Jun;12(6):852-858.

MOST STUDY



n = 124





Median TTF (month)
Gefitinib: 14.6
Erlotinib: 22.9
Afatinib: 15.3

Pasello G et al. *Oncologist*. 2019 Mar 7. pii: theoncologist.2018-0712. doi: 10.1634/theoncologist.2018-0712.

Duration of treatment among patients prescribed afatinib or erlotinib as first-line therapy for EGFR mutation-positive non-small-cell lung cancer in the USA

Jonathan Lim*,[1], Carl Samuelsen[2], Amanda Golembesky[2], Sulena Shrestha[3], Li Wang[3] & Ingolf Griebsch[2]

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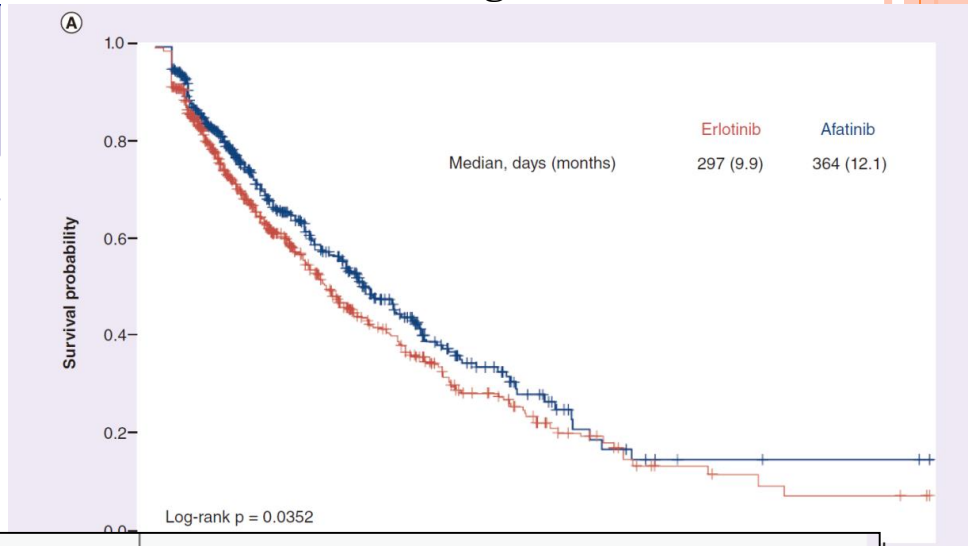
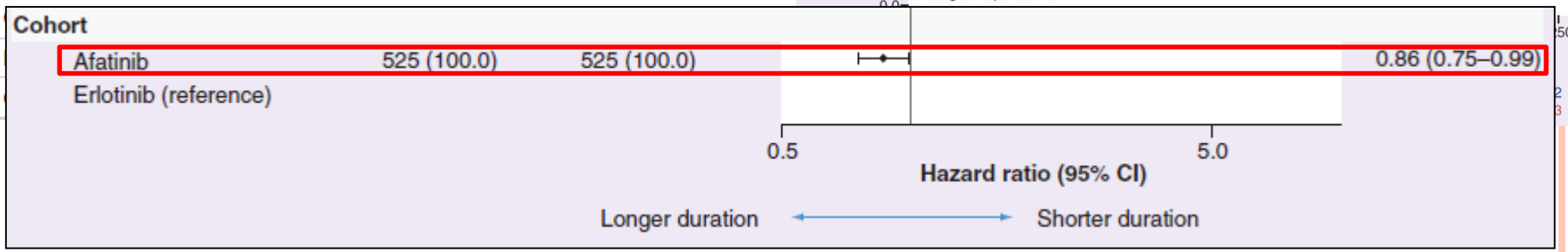
[2]Boehringer Ingelheim International GmbH, Ingelheim, Germany
[3]STATinMED Research, Plano, TX 75024, USA
*Author for correspondence: jonathan.lim@boehringer-ingelheim.com

2013 – 2017
US data base
Propensity-score matching

Demographic and clinical characteristics	Before matching		
	Erlotinib (N = 2602)	Afatinib (N = 550)	p-value
Age, years, mean ± SD	67.1 (12.0)	63.3 (11.4)	<0.001
Individual comorbidities; n (%):			
– Cerebrovascular disease	429 (16.5)	60 (10.9)	0.001
– Coronary heart disease	373 (14.3)	71 (12.9)	0.382
– Myocardial infarction	108 (4.2)	16 (2.9)	0.174
– Heart failure	204 (7.8)	30 (5.5)	0.053
– Peripheral arterial disease	295 (11.3)	44 (8.0)	0.022
– Diabetes mellitus	520 (20.0)	96 (17.5)	0.174





Lim J et al. *Future Oncol*. 2019 May;15(13):1493-1504.

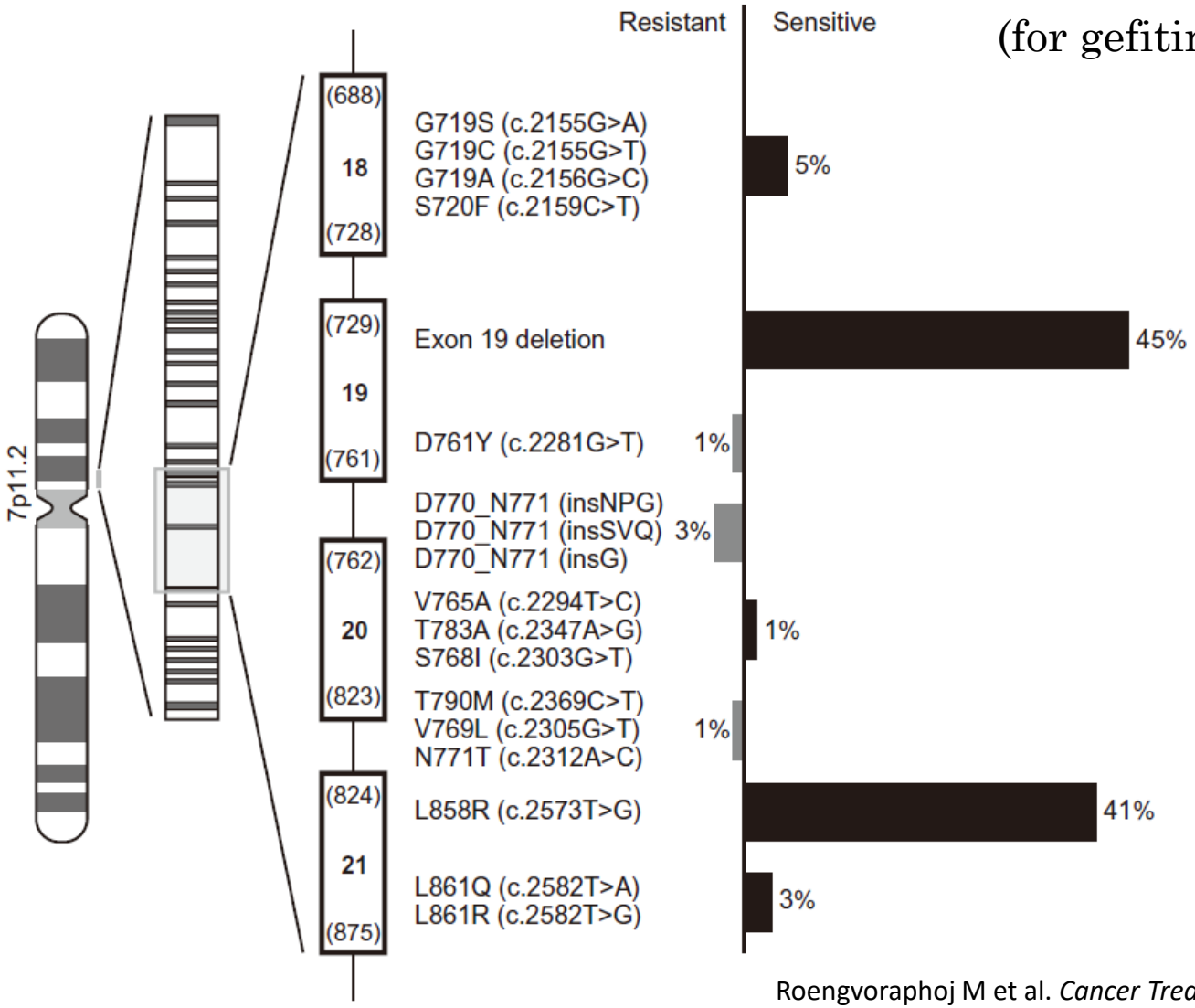
Real-world First-line EGFR TKI

- Physicians tend to use gefitinib in patients with
  - Older age
  - Never smoker
  - Poorer performance
- Physicians tend to use afatinib in patients with
  - Younger age
  - Smoker
  - Exon 19 deletion
  - Uncommon EGFR mutation
- The PFS difference among the 3 TKIs varied in different studies.

Uncommon EGFR mutations

Uncommon EGFR mutations

(for gefitinib and erlotinib)



Roengvoraphoj M et al. *Cancer Treat Rev*. 2013 Dec;39(8):839-50.

Table 2. Summary of the *in vitro* sensitivities of Ba/F3 cells expressing each EGFR mutation to various TKI

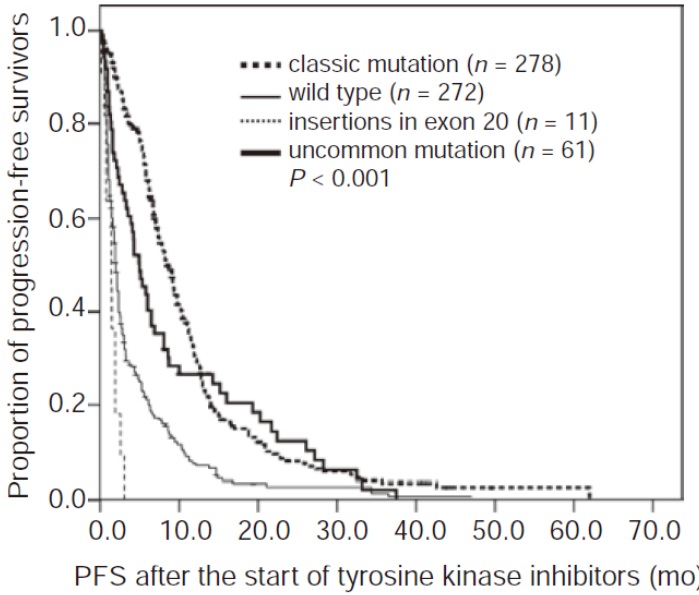
Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750	4.8	4.9	0.9	<1	60	1.1	19
	Del19	delE746_S752insV	306	14	0.2	1.4	86		
	Del19	delL747_A750insP	7.4	13	1	1.6	30		
	Del19	delL747_P753insS	4.1	5.4	2	1.9	38		
	Del19	delS752_I759	35	7.9	0.2	2	6.7		
	Ins19	I744_K745insKIPVAI	400		7				
	Ins19	K745_E746insTPVAIK	100		0.9				
20	Ins20	A763_Y764insFQEA	174	48	3.7			44	673
	Ins20	Y764_V765insHH	>1000	3845	79			237	1730
	Ins20	M766_A767insAI		3403	79				
	Ins20	V769_D770insASV	3100	4400	72	230	48	333	5290
	Ins20	D770_N771insNPG	3356	3700	72		230	42	262
	Ins20	D770_N771insSVD		3187	86				
	Ins20	H773_V774insH		>10 000	268		550		
	S768I	S768I	315	250	0.7			49	
	T790M	T790M+delE746_A750	8300	>10 000	64	140		3	28
	T790M	T790M+L858R	>10 000	>10 000	119	300		21	13
21	L858R	L858R	26	16	4	2.6	1.4	9	140
	L861Q	L861Q	170	103	0.5		3.3	9	
EGFR wild type with interleukin-3			9350	>10 000	>100	>1000	>1000	3078	1549
Plasma drug concentration			(448–2717)	(2717–4040)	(69–130)	(166–238)	(N/A–132)	(400–600)	N/A–N/A

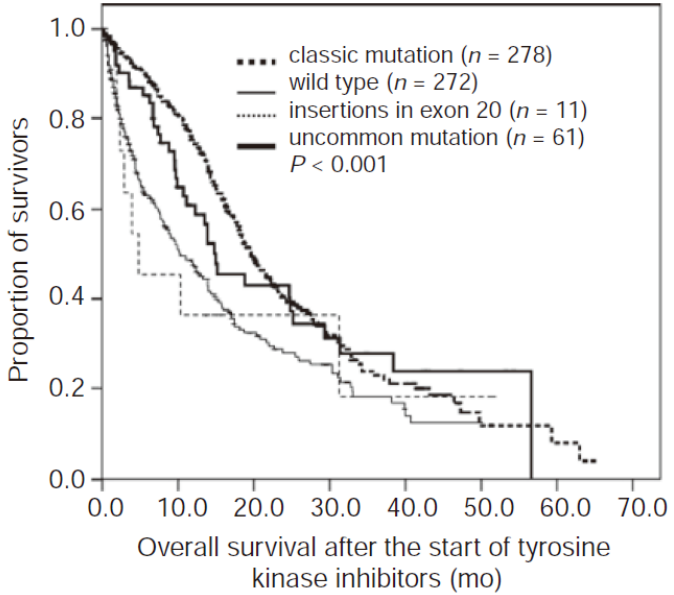
IC50 values (nM) of <10, 10–99, 100–999 and ≥1000 are shown in blue, light blue, yellow and red, respectively. When the exact value was not described in the literature, the approximate number was estimated from each figure. IC90 values are described in del709_T710insD, E709K, G719A and wild type. EGFR, epidermal growth factor receptor; N/A, not availabe TKI, tyrosine kinase inhibitors.

Kobayashi Y et al. *Cancer Sci*. 2016 Sep;107(9):1179-86.

Gefitinib or Erlotinib for Uncommon EGFR mutation other than T790M

No. of patients	*EGFR* mutation	RR (%)	PFS (mo)	OS (mo)
278	Single classical mutation (deletions in exon 19 or L858R)	74.1	8.5	19.6
272	Wild type	16.5	2.0	10.4
11	Insertions in exon 20	0	1.4	4.8
15	G719 (single or complex)	53.3	8.1	16.4
15	L861 (single or complex)	60.0	6.0	15.2
20	Uncommon mutations with combination with deletions in exon 19 or L858R	60.0	5.3	18.8
15	Uncommon mutations without combination with deletions in exon 19 or L858R or G719 or L861	20.0	1.6	11.1

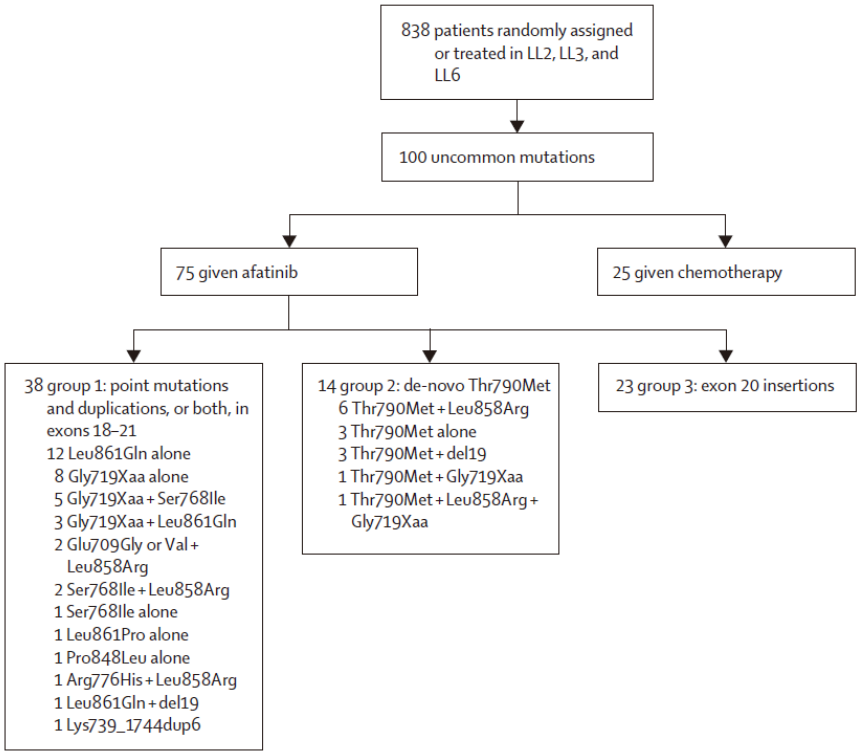


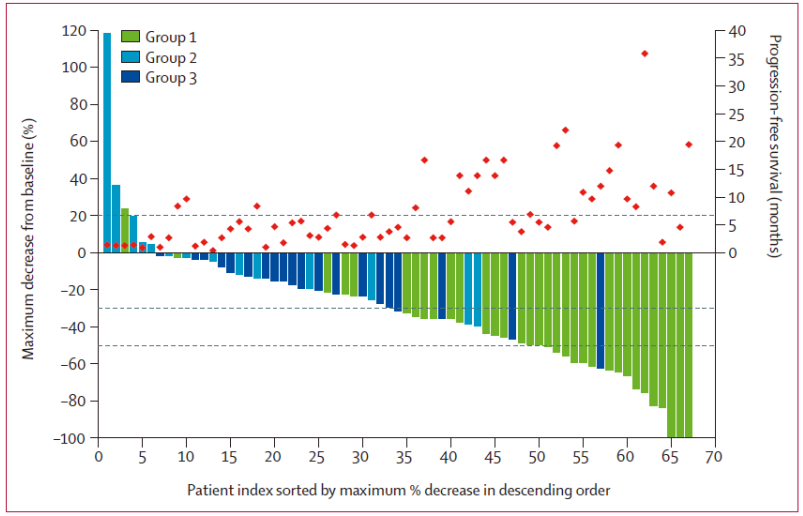


Wu JY et al. *Clin Cancer Res*. 2011 Jun 1;17(11):3812-21.

Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

James C-H Yang, Lecia V Sequist*, Sarayut Lucien Geater, Chun-Ming Tsai, Tony Shu Kam Mok, Martin Schuler, Nobuyuki Yamamoto, Chong-Jen Yu, Sai-Hong I Ou, Caicun Zhou, Daniel Massey, Victoria Zazulina, Yi-Long Wu*





	Mutation	Objective response	Progression-free survival (months)	Overall survival (months)
Gly719Xaa (n=18)	Gly719Xaa (n=8) Gly719Xaa+Thr790Met (n=1) Gly719Xaa+Ser768Ile (n=5) Gly719Xaa+Leu861Gln (n=3) Gly719Xaa+Thr790Met+Leu858Arg (n=1)	14 (77·8%, 52·4–93·6)	13·8 (6·8–NE)	26·9 (16·4–NE)
Leu861Gln (n=16)	Leu861Gln (n=12) Leu861Gln+Gly719Xaa (n=3) Leu861Gln+Del19 (n=1)	9 (56·3%, 29·9–80·2)	8·2 (4·5–16·6)	17·1 (15·3–21·6)
Ser768Ile (n=8)	Ser768Ile (n=1) Ser768Ile+Gly719Xaa (n=5) Ser768Ile+Leu858Arg (n=2)	8 (100·0%, 63·1–100·0)	14·7 (2·6–NE)	NE (3·4–NE)

Data are n (%, 95% CI) or median (95% CI). NE=not estimable. Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

Table 3: **Activity of afatinib in specific compound uncommon mutations**

Yang JC et al. *Lancet Oncol*. 2015 Jul;16(7):830-8.

Real world EGFR TKIs against uncommon EGFR mutations

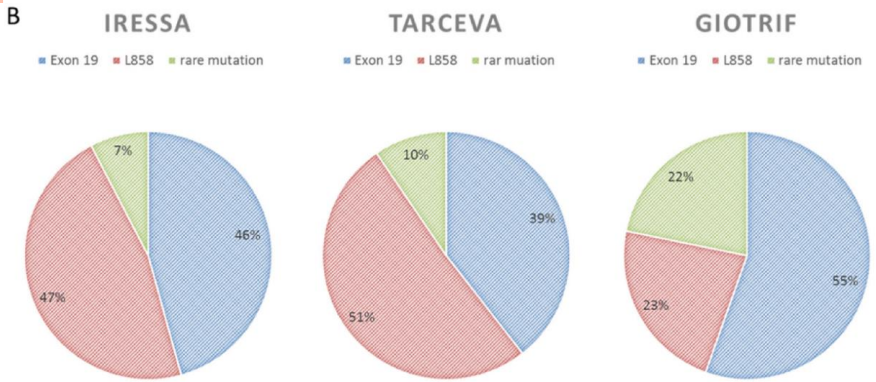
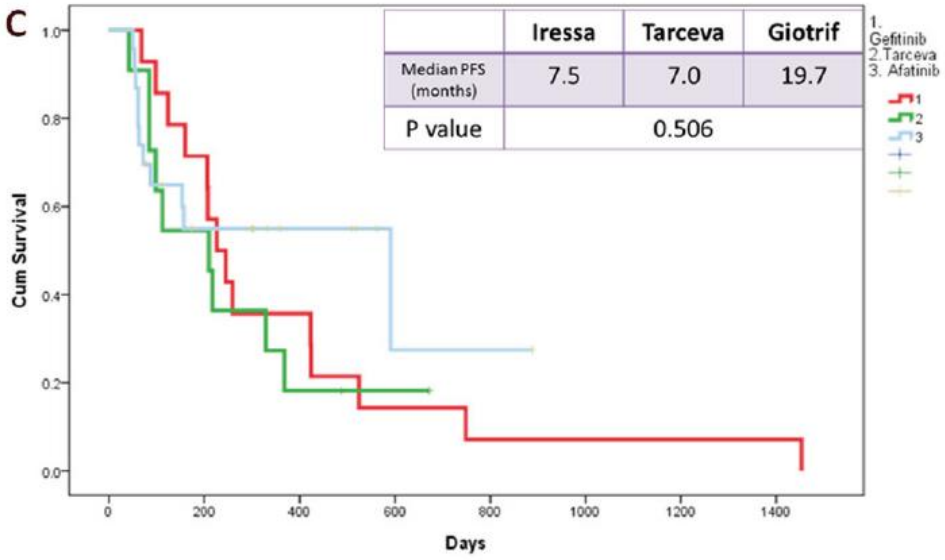
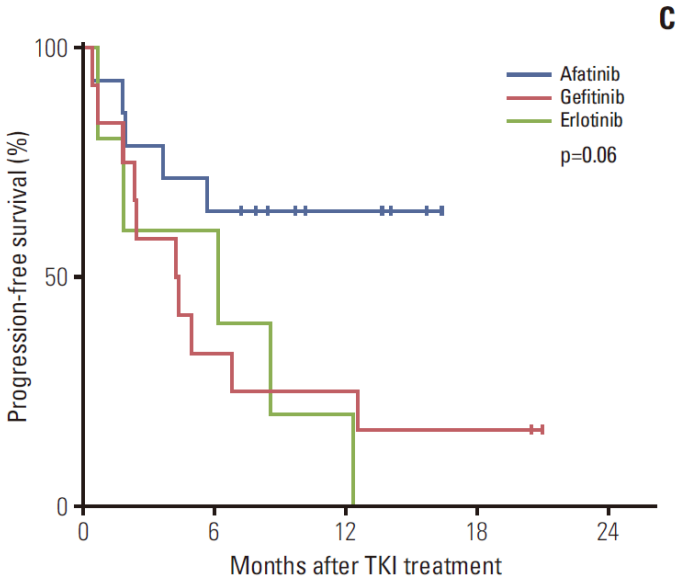


Table 2. Objective response rates according to uncommon *EGFR* mutation

EGFR TKI	Afatinib		Gefitinib		Erlotinib	
	Total	Objective response	Total	Objective response	Total	Objective response
Uncommon *EGFR* mutation	14	8	12	4	5	1
Uncommon *EGFR* mutation other than T790M	10	8	9	4	5	1
Uncommon *EGFR* mutation						
Exon 21 L858R+exon 20 T790M	3	0	3	0	0	0
Exon 19 deletion+exon 20 T790M	1	0	0	0	0	0
Exon 21 L861 Q	3	3	4	2	0	0
Exon 18 G719X	3	2	4	2	3	1
Exon 20 insertion	1	0	0	0	2	0
Exon 18 G719X+exon 20 S768I	1	1	1	0	0	0
Exon 19 Deletion+L747_P753>Q	1	1	0	0	0	0
Exon 21 L858R+H870R	1	1	0	0	0	0

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.





Tu CY et al. *Oncotarget*. 2018 Feb 4;9(36):24237-24247.
Kim Y et al. *Cancer Res Treat*. 2019 Apr;51(2):502-509.

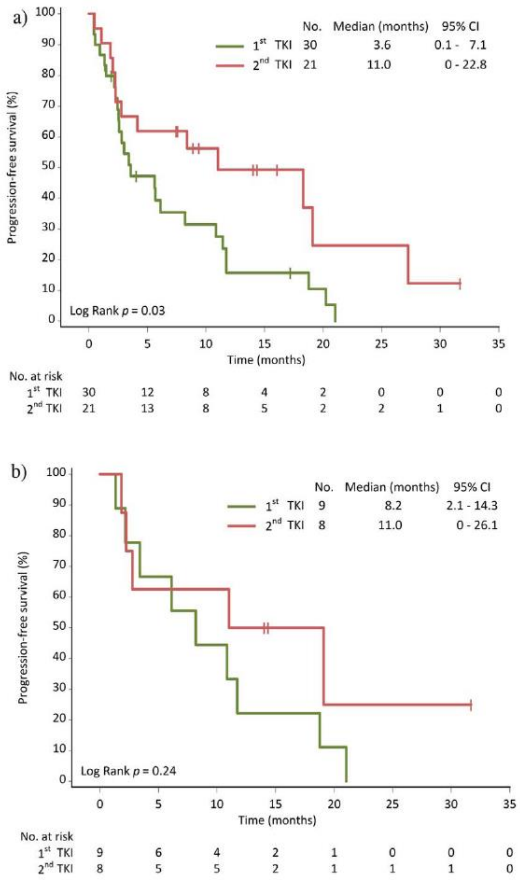
Real world EGFR TKIs against uncommon EGFR mutations

Non-classical *EGFR* Mutations present in this study.

Group	Mutation	Number (%)
Group 1	20 insertions	5 (8.9)
Group 2	Non-classical mutation with Del19 or L858R complex mutations	17 (30.4)
	Del19 + 18G721D	1
	Del19 + 19L732P	1
	Del19 + 20L792P	1
	Del19 + 20S768I + 20V774M	1
	Del19 + 21L858R + 21K860I	1
	21L858R + 18E709X	1
	21L858R + 20S768I	1
	21L858R + 20V786E	1
	21L858R + 20T790M	5
	21L858R + 20 insertion	1
	21L858R + 21L833V	1
	21L858R + 21K860I	1
	21L858R + 18G719X + 20 insertion	1
Group 3	Non-classical mutation alone or in combination with other non-classical mutations	34 (60.7)
	18I715V	1
	18K716E	1
	18V717G	1
	18G719X	8
	19L747P	1
	19 insertion	1
	20A763_Y764 insFQEA	2
	20S768I	2
	20G779F	1
	21L861Q	5
	18G719X + 21L861Q	1
	18E709X + 18G719X	4
	18G719X + 20S768I	1
	20T790 M + 21L861Q	1
	21M825L + 21R831C	1
	18V703L + 18L707W + 18G719X	1
	18E709X + 18T710S + 18G719X	1
	19V742F + 19A743 V + 20H773R	1

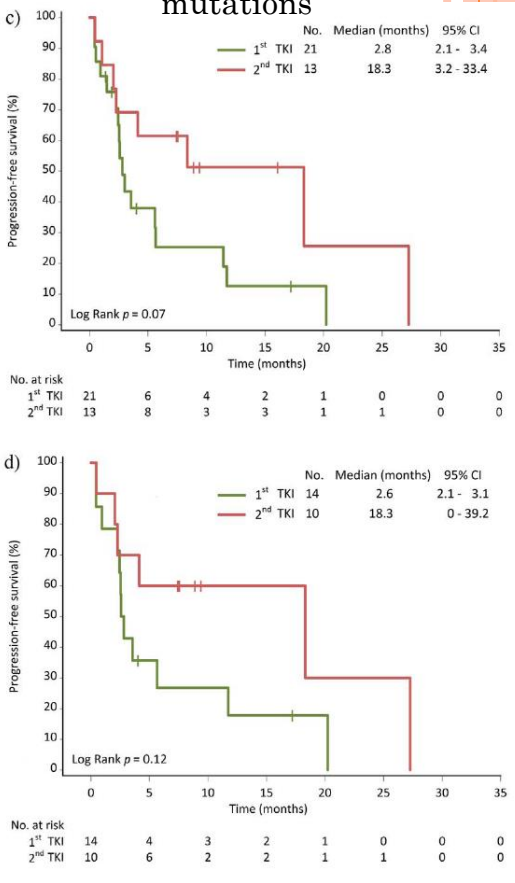
T790M was excluded.

entire non-classical mutations cohort



non-classical without classical mutations

non-classical with classical mutations



G719X, S768I, or L861Q

Shen YC et al. *Lung Cancer*. 2017 Aug;110:56-62.

First-line EGFR TKI PFS in NTUH cohort

Table 2. Progression-free Survival: Univariate and Multivariate Analysis (n = 301)

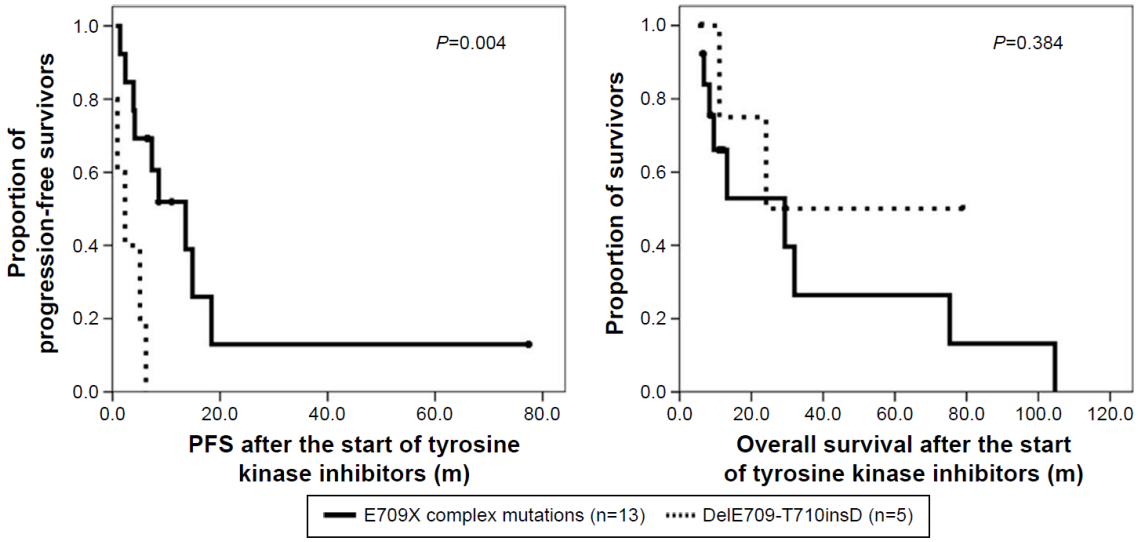
	Univariate analysis			Multivariate analysis		
Variable	**Hazard ratio**	**95% CI**	***p* Value**	**Adjusted hazard ratio**	**95% CI**	***p* Value**
Age (≥70)	1.06	0.80–1.41	0.67			
Male sex	1.06	0.79–1.41	0.72			
Never-smoker	0.79	0.58–1.09	0.15			
ECOG ≥2	2.13	1.38–3.30	0.001	1.73	1.09–2.75	0.02
Post-operative recurrence	0.62	0.42–0.91	0.02	0.69	0.46–1.03	0.07
EGFR mutation						
Exon 19 deletion	1.00[2]		0.004	1.00[2]		0.01
L858R	1.20	0.89–1.62	0.23	1.13	0.82–1.56	0.44
Uncommon mutation[1]	2.14	1.37–3.33	0.001	2.02	1.27–3.21	0.003
EGFR TKI						
Gefitinib	1.00[3]		0.67	1.00[3]		0.46
Erlotinib	0.85	0.59–1.22	0.38	0.78	0.52–1.18	0.25
Afatinib	0.94	0.68–1.29	0.68	0.84	0.59–1.21	0.84
M1a or intrathoracic recurrence	0.66	0.48–0.89	0.007	0.82	0.58–1.16	0.27
Initial brain metastasis	1.39	1.02–1.88	0.04	1.27	0.87–1.84	0.21
Initial liver metastasis	1.55	1.03–2.35	0.04	1.45	0.94–2.25	0.09

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

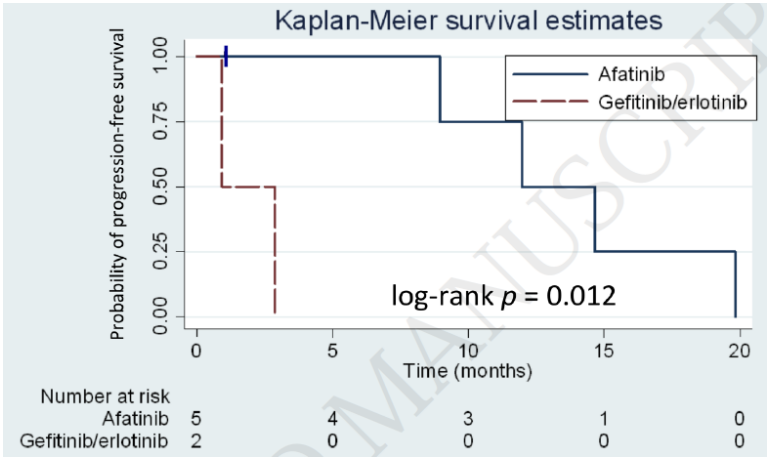
RARE EGFR TKI-SENSITIVE MUTATION

- E709X

1st G EGFR TKI
RR 50%, mPFS 6.2m, OS 29.3m



- L747P, L747S



Wu JY et al. *Onco Targets Ther*. 2016 Oct 11;9:6137-6145.

1st G EGFR TKI
RR 0%, mPFS 0.92m

Afatinib
RR 80%, mPFS 11.97m

Liang SK et al. *Lung cancer*. Accepted Manuscript. https://doi.org/10.1016/j.lungcan.2019.05.019

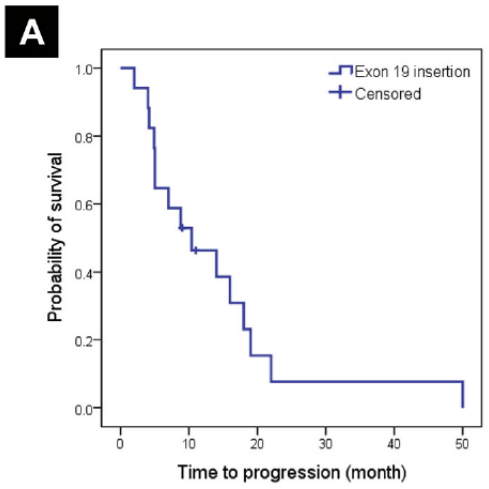
RARE EGFR TKI-SENSITIVE MUTATION

- Exon 19 insertion

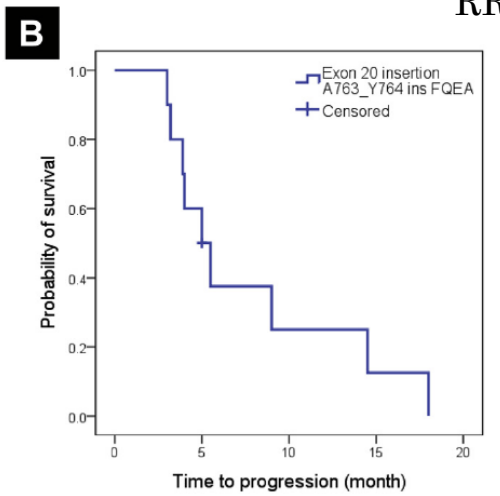
	Nucleotide sequence and amino acid sequence	Nucleotide change	Amino acid change	Reference
Wild type	2215 2219 2234 ↓ ↓ ↓ GTTAAAATTCCCGTCGCTATCAAGGAATTAAGAGAA V K I P V A I K E L R E 738 740 744745 747	Wild type	Wild type	
Exon 19 insertion Type 1 (n=7)	2215 ↓ GTTAAAATTCCCGTCGCTATC*AAAATTCCCGTCGCTATC*AAG V K I P V A I ***K I P V A I*** K 738 744 747 (745)	c.2215-2232dup	p. I744_K745 insKIPVAI	Current study, 14
Exon 19 insertion Type 2 (n=7)	2213 ↓ GTTAAAATTCCCGTCGCTA*TTAAAATTCCCGTCGCTA*TTAAG V K I P V A I ***K I P V A I*** K 738 744 747 (745)	c.2213-2230dup	p. I744_K745 insKIPVAI	14, 15, 16, 30
Exon 19 insertion Type 3 (n=1)	2219 ↓ ATTCCCGTCGCTATCAAGG*TTCCCGTCGCTATCAAGG*AATTA I P V A I K ***V P V A I K*** E L 740 745 747 (746)	c.2219-2236dup	p. K745_E746 insVPVAIK	14
Exon 19 insertion Type 4 (n=1)	2215 2234 ↓ ↓(------18 base pairs-----) GTTAAAATTCCCGTCGCTATCAA*AAcTCCCGTCGCTATCAA*GGAA V K I P V A I K ***T P V A I K*** E 738 744745 747 (746)	c.2234-2235ins18	p.K745_E746 insTPVAIK	14

- Exon 20 insertion (A763_Y764 insFQEA)

	Nucleotide sequence and amino acid sequence	Nucleotide change	Amino acid change	Reference
Wild type	2290 ↓ GAAGCCTACGTGATGGCC E A Y V M A 762 763 764	Wild type	Wild type	
Exon 20 A763_Y764 insFQEA (n=8)	2290 ↓ GAAGCCT*TCCAGGAAGCCT*ACGTGATGGCC E A ***F Q E A*** Y V M A 762 763 (764)	c.2290_2291 ins *TCCAGGAAGCCT*	p. A763_Y764 insFQEA	Current study, 19, 20, 38



1st G EGFR TKI
RR 56%, mTTP 10.4m



1st G EGFR TKI
RR 73%, mTTP 5.0m

Lin YT et al. *Clin Lung Cancer*. 2017 May;18(3):324-332.e1.

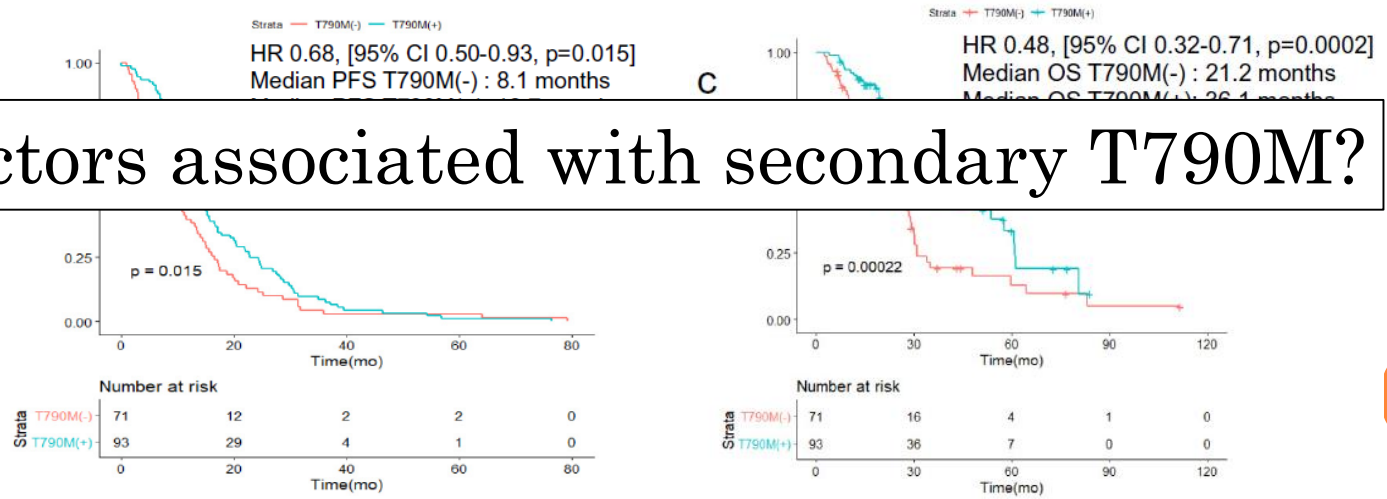
Uncommon EGFR mutation

- PFS of EGFR TKIs are shorter for uncommon EGFR mutation than for classical EGFR mutation.
- Afatinib may be better than gefitinib or erlotinib for against uncommon EGFR mutation.
- Several rare EGFR mutations may be still EGFR TKI-sensitive.
  - E709X
  - L747P, L747S (afatinib)
  - Exon 19 insertion
  - Exon 20 insertion (A763_Y764 insFQEA)

Secondary T790M mutation

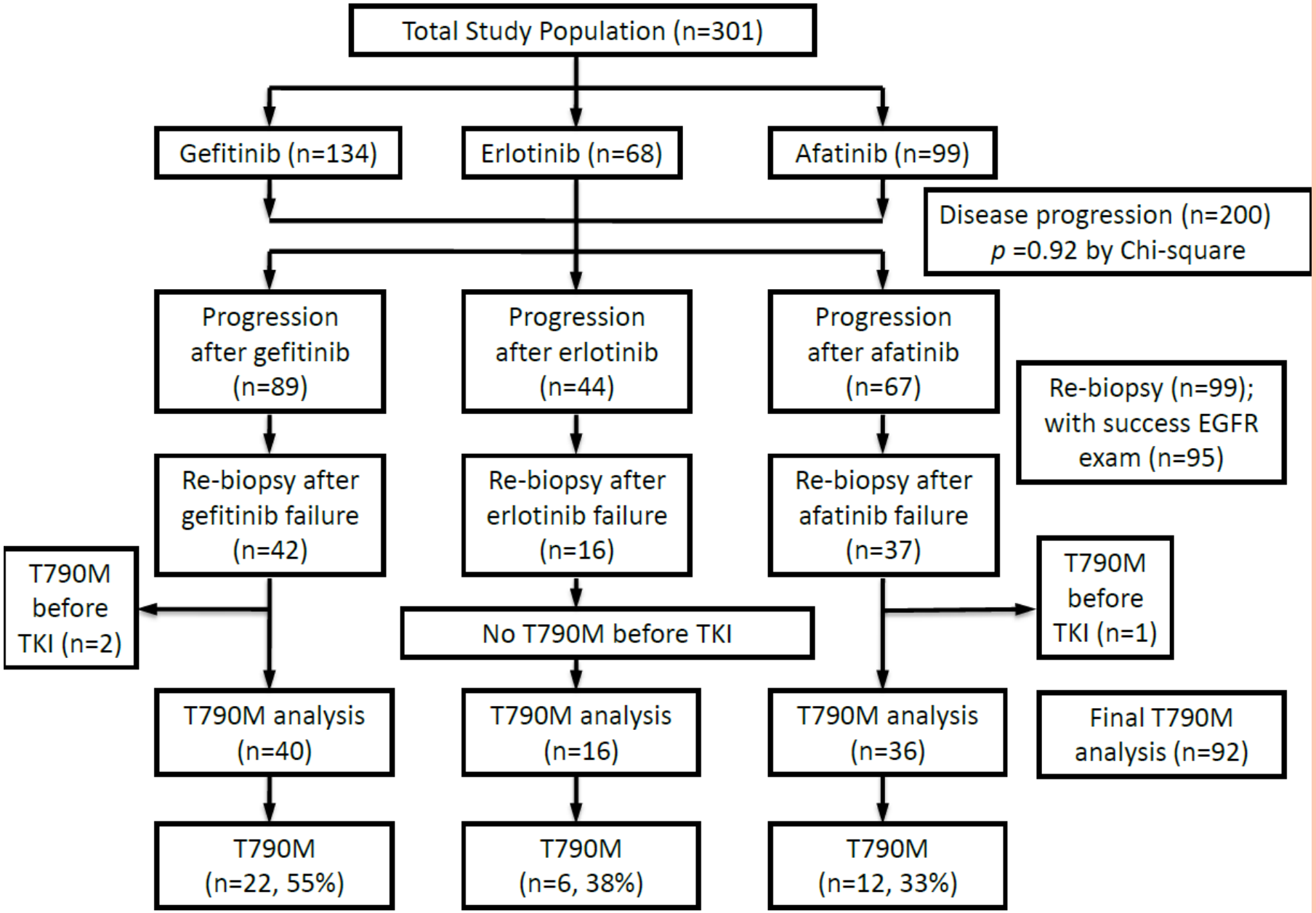
Secondary T790M

- Accounting for around 50% EGFR TKI resistance
  - Gefitinib — Kobayashi S et al. *N Engl J Med*. 2005 Feb 24;352(8):786-92.
  - Erlotinib — Pao W et al. *PLoS Med*. 2005 Mar;2(3):e73.
  - Afatinib — Wu SG et al. *Oncotarget*. 2016 Mar 15;7(11):12404-13.
- Tumors with T790M tends to grow slower.
- Patients with T790M have better TKI PFS and OS.



Factors associated with secondary T790M?

Yoon BW et al. *Transl Oncol*. 2019 Jun;12(6):852-858.


Total Study Population (n=301)
Gefitinib (n=134)
Erlotinib (n=68)
Afatinib (n=99)
Disease progression (n=200)
p =0.92 by Chi-square
Progression after gefitinib (n=89)
Progression after erlotinib (n=44)
Progression after afatinib (n=67)
Re-biopsy (n=99); with success EGFR exam (n=95)
Re-biopsy after gefitinib failure (n=42)
Re-biopsy after erlotinib failure (n=16)
Re-biopsy after afatinib failure (n=37)
T790M before TKI (n=2)
No T790M before TKI
T790M before TKI (n=1)
T790M analysis (n=40)
T790M analysis (n=16)
T790M analysis (n=36)
Final T790M analysis (n=92)
T790M (n=22, 55%)
T790M (n=6, 38%)
T790M (n=12, 33%)

Patients with Adequate Tissue for Rebiopsy* (n=92)

Variable	Secondary T790M (n=40)	No secondary T790M (n=52)	Total Rebiopsied patients (n=92)	*p value (between with/without 2nd T790M)*
Median age (year-old) (IQR)	65 (58-71)	66 (55-73)	66 (57-73)	0.96
Male	19 (48%)	18 (35%)	37 (40%)	0.21
Never smoker	36 (90%)	37 (71%)	67 (73%)	0.68
Adenocarcinoma	40 (100%)	50 (96%)	90 (98%)	0.46
Initial EGFR mutation				0.06
Del 19	22 (55%)	20 (39%)	42 (46%)	
L858R	16 (40%)	22 (42%)	38 (41%)	
G719X, L861X, S768	0 (0%)	8 (15%)	8 (9%)	
T790M	0 (0%)	0 (0%)	0 (0%)	
Del 19 or L858R or G719X AND T790M	0 (0%)	0 (0%)	0 (0%)	
Other Complex	2 (5%)	2 (4%)	4 (4%)	
Others	0 (0%)	0 (0%)	0 (0%)	
First line EGFR TKI				0.14
Gefitinib	22 (55%)	18 (35%)	40 (44%)	
Erlotinib	6 (15%)	10 (19%)	16 (17%)	
Afatinib	12 (30%)	24 (46%)	36 (39%)	
Cancer status before EGFR TKI				0.43
Post-operative or post-CCRT recurrence	6 (15%)	5 (10%)	11 (12%)	
Stage IV	34 (85%)	47 (90%)	81 (88%)	
ECOG 0-1 before 1st line EGFR TKI	39 (98%)	48 (92%)	87 (95%)	0.28
Initial M1a disease or intrathoracic recurrence only	13 (33%)	16 (31%)	29 (32%)	0.86
Initial brain metastasis	5 (13%)	15 (29%)	20 (22%)	0.06
Initial bone metastasis	15 (38%)	20 (39%)	35 (38%)	0.93
Initial liver metastasis	9 (23%)	4 (8%)	13 (14%)	0.04
First line EGFR TKI Duration (month) (IQR)	15.1 (8.3-17.2)	10.7 (6.4-15.2)	11.8 (6.9-16.6)	0.02

*Patients with initial EGFR T790M mutation before TKI treatment were excluded.

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

Factors associated with secondary T790M

Table 4. Logistic Regression for Secondary T790M: Univariate and Multivariate analysis (n = 92)

	Univariate analysis			Multivariate Backward LR model		
Variable	**Odds ratio**	**95% CI**	***p* Value**	**Adjusted odds ratio**	**95% CI**	***p* Value**
Age (≥ 70)	1.11	0.46–2.65	0.82			
Male	1.71	0.74–3.97	0.21	3.25	1.10–9.66	0.034
Never-smoker	1.22	0.48–3.09	0.68			
EGFR mutation						
Exon 19 deletion	1.00[1]		0.11	1.00[1]		0.10
L858R	0.66	0.27–1.60	0.36	0.47	0.16–1.36	0.16
Uncommon mutation[2]	0.18	0.04–0.93	0.04	0.14	0.02–0.97	0.047
Gefitinib[3]	2.31	0.99–5.38	0.05	3.29	1.15–9.46	0.027
1st-line EGFR TKI duration ≥13 months	3.34	1.40–7.95	0.006	3.16	1.20–8.33	0.020
Initial brain metastasis	0.35	0.12–1.07	0.07			
Initial liver metastasis	3.48	0.99–12.30	0.052	4.97	1.18–20.96	0.029

Independent factors from the study:
Male, uncommon EGFR mutation, first-line gefitinib, EGFR TKI duration and initial liver metastasis

Lin YT et al. *Int J Cancer*. 2019 Jun 1;144(11):2887-2896.

SECONDARY T790M IN THE REAL WORLD (II)

Table 3 Univariate Analysis of Clinical Course and Treatment History (n = 125)

	T790M-positive (n = 55)	T790M-negative (n = 70)	*P* Value
Total duration of EGFR-TKI treatment before rebiopsy, mo (range)	21 (1-62)	13 (1-90)	.03
TKI-free interval, d (range)	0 (0-876)	21 (0-873)	.01
TKI treatment history immediately before rebiopsy			.03
Yes	45	45	
No	10	25	
Previous EGFR-TKI treatment (total)			
Gefitinib	38	48	.95
Erlotinib	27	33	.83
Others	2	6	.26
Beyond-PD treatment with initial EGFR-TKI, d (range)	21 (0-847)	5 (0-625)	.02
PFS on initial EGFR-TKI treatment, mo (range)	15 (1-61)	11 (1-100)	.03
Response to initial EGFR-TKI treatment			.12
Complete response	0	0	
Partial response	43	44	
Stable disease/ progressive disease	12	24	
Overall survival, mo (range)	16 (8-23)	7 (5-12)	.04

Figure 1 Incidence of T790M (%)

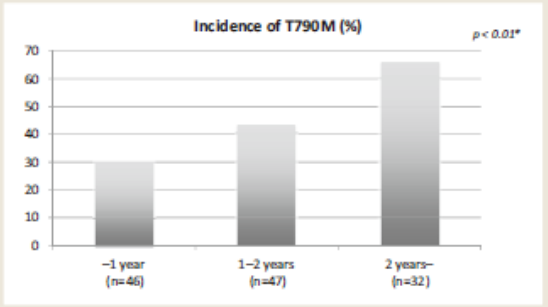


Table 5 Multivariate Analysis of Clinical Course and Treatment History (n = 125)

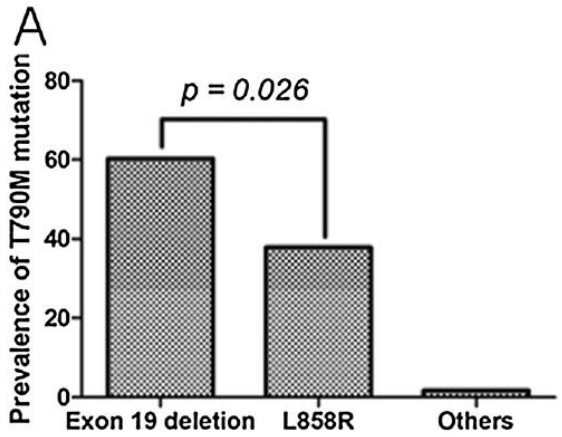
Variables	Multivariate Analyses OR (95% CI)	*P*
Surgical history (Postsurgery recurrence vs. advanced)	4.15 (1.28-15.7)	.02
Total EGFR-TKI treatment duration (≥1 y vs. <1 y)	4.41 (1.13-19.8)	.03
TKI-free interval (<1 mo vs. ≥1 mo)	1.81 (0.50-6.80)	.36
TKI treatment history immediately before rebiopsy (Yes vs. no)	1.09 (0.30-3.83)	.90
Beyond-PD treatment with initial EGFR-TKI (≥1 mo vs. <1 mo)	1.81 (0.70-4.77)	.22
PFS on initial TKI treatment (<1 y vs. ≥1 y)	3.25 (0.85-14.4)	.09
Rebiopsy sites: fluid (No vs. yes)	2.14 (0.95-4.95)	.07

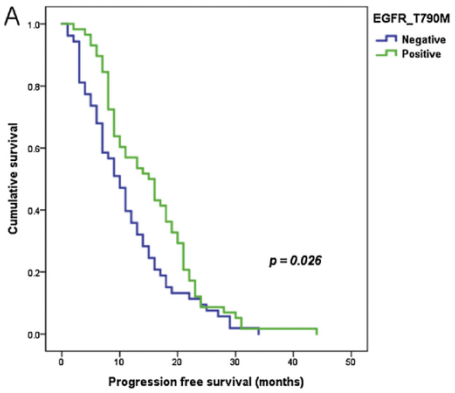
Kawamura T et al. *Clin Lung Cancer*. 2018 Mar;19(2):e247-e252.

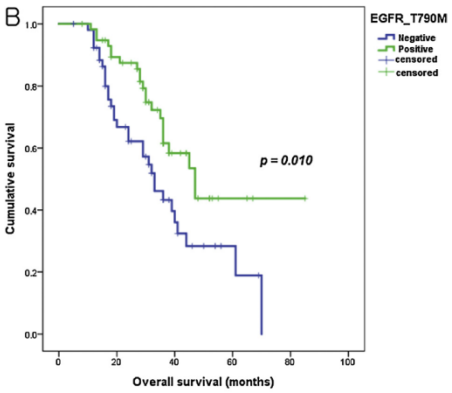
SECONDARY T790M IN THE REAL WORLD (III)

Table 1
Patient characteristics according to T790M mutation status.

Variables	All, n (%)	T790 M positive, n (%)	T790 M negative, n (%)	p-value
Number of cases	111 (100.0)	58 (52.3)	53 (47.7)	
Age, mean (range)	59.4 (25–80)	59.5 (25–80)	59.4 (31–79)	0.948
< 60 years	52 (46.8)	27 (46.6)	25 (47.2)	
≥60 years	59 (53.2)	31 (53.4)	28 (52.8)	
Sex				0.174
Male	45 (40.5)	20 (34.5)	25 (47.2)	
Female	66 (59.5)	38 (65.5)	28 (52.8)	
Smoking history				0.467
Non-smoker	77 (69.4)	42 (72.4)	35 (66.0)	
Smoker	34 (30.6)	16 (27.6)	18 (34.0)	
EGFR mutation type at 1st biopsy				0.017
Exon 19 deletion	54 (48.6)	35 (60.3)	19 (35.8)	
L858R	51 (45.9)	22 (37.9)	29 (54.7)	
Others	6 (5.4)	1 (1.7)	5 (9.4)	
Extrathoracic metastasis				0.476
Present	98 (88.3)	50 (86.2)	48 (90.6)	
Absent	13 (11.7)	8 (13.8)	5 (9.4)	
EGFR-TKI				0.924
Gefitinib	80 (72.1)	41 (70.7)	39 (73.6)	
Erlotinib	27 (24.3)	15 (25.9)	12 (22.6)	
Afatinib	4 (3.6)	2 (3.4)	2 (1.8)	
Line of initial EGFR-TKI				0.471
First	71 (64.0)	34 (58.6)	37 (69.8)	
Second	35 (31.5)	21 (36.2)	14 (26.4)	
Third	5 (4.5)	3 (5.2)	2 (3.8)	
Interval between prior EGFR-TKI and rebiopsy				0.036
< 12 months	24 (21.6)	8 (13.8)	16 (30.2)	
≥12 months	87 (78.4)	50 (86.2)	37 (69.8)	
Total duration of EGFR-TKI treatment				0.015
< 14 months	60 (54.1)	25 (43.1)	35 (66.0)	
≥14 months	51 (45.9)	33 (56.9)	18 (34.0)	
SCLC transformation				0.008
Present	6 (5.4)	0 (0.0)	6 (11.3)	
Absent	105 (94.6)	58 (100.0)	47 (88.7)	
Survival				0.030
Alive	58 (52.3)	36 (62.1)	22 (41.5)	
Dead	53 (47.7)	22 (37.9)	31 (58.5)	







Joo JW T et al. *Lung Cancer*. 2018 July;121:12-17.

Table 1. Patients' characteristics and demographic data

Characteristic	No. (%) (n=205)
Age, median (range, yr)	60 (32-88)
Sex	
Male	76 (37.1)
Female	129 (62.9)
Smoking status	
Never smokers	162 (79.0)
Former smokers	23 (11.2)
Current smokers	20 (9.8)
Baseline *EGFR* mutation status	
Exon 19 deletions	111 (54.1)
Exon 21 L858R	83 (40.5)
Other mutations[a)]	11 (5.4)
First-line TKI	
Gefitinib	94 (45.9)
Erlotinib	98 (47.8)
Afatinib	13 (6.3)
Best response of first-line TKI	
Stable disease	29 (14.1)
Partial response	176 (85.9)
PFS of first-line TKI	
≤ 11 mo	107 (52.2)
> 11 mo	98 (47.8)
Rebiopsy site	
Primary tumor	68 (33.2)
Metastases	137 (66.8)

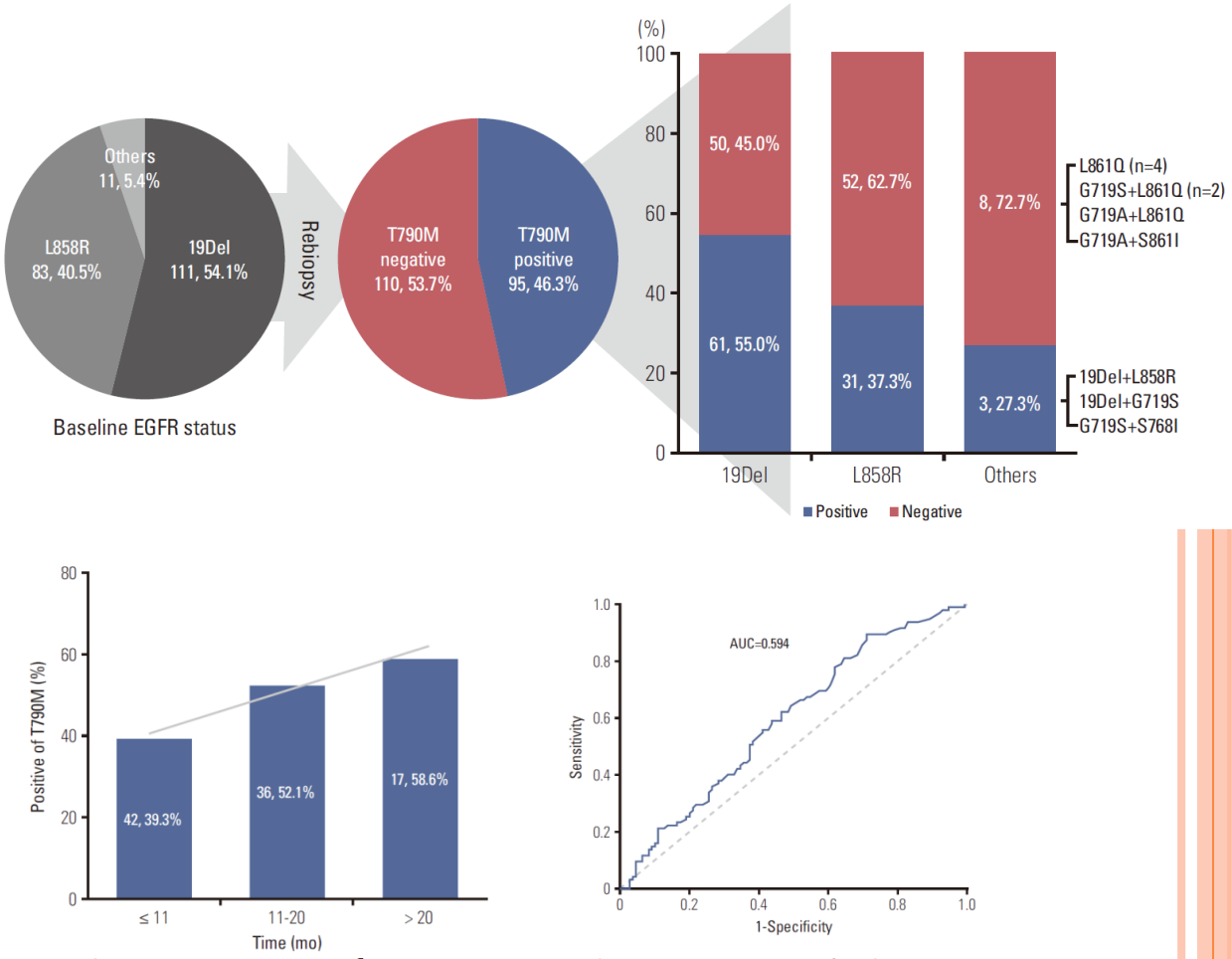
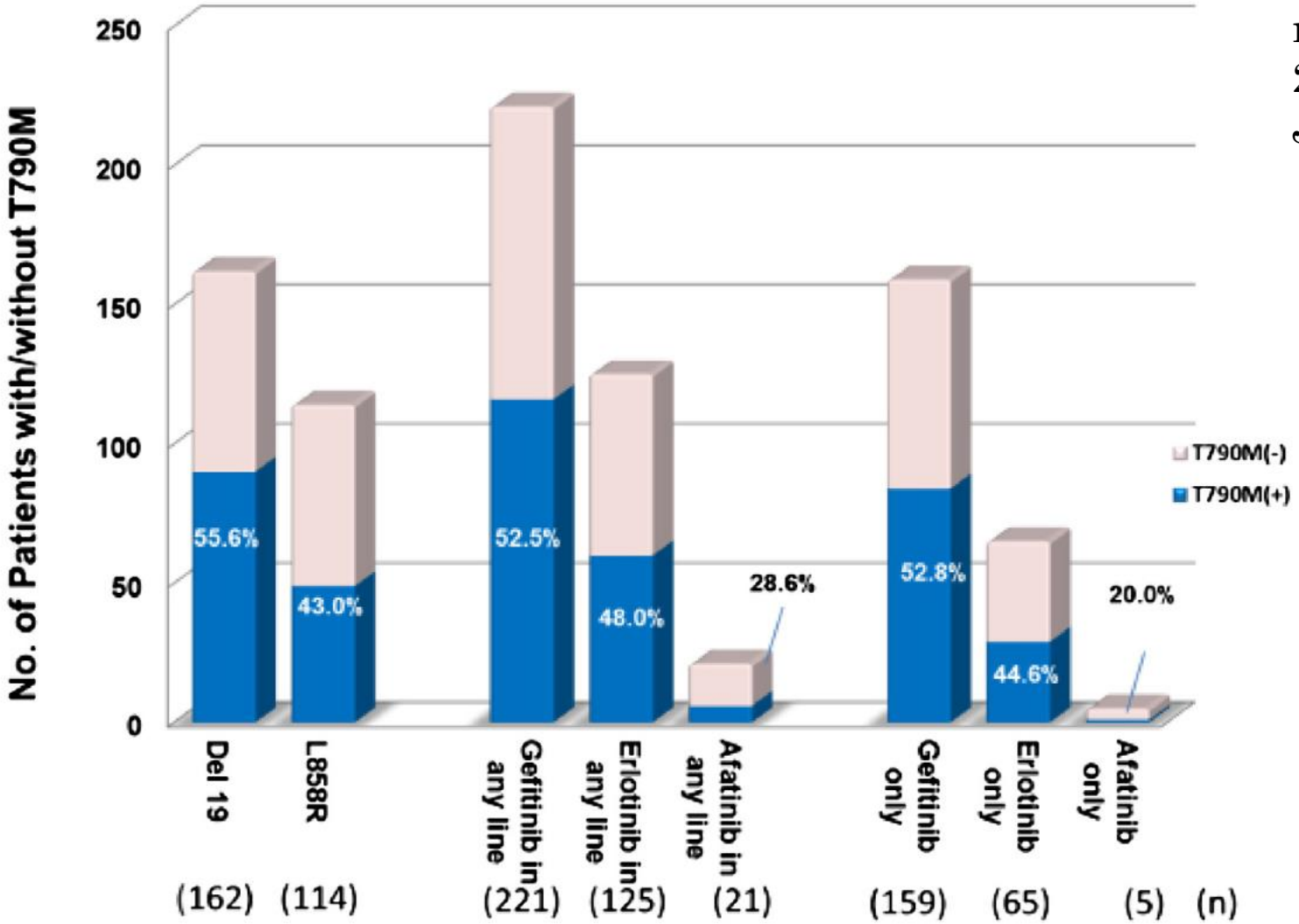


Table 3. Multivariate analysis of the association between patients' characteristics and T790M status of rebiopsy

Characteristic	Odds ratio (95% CI)	p-value[a)]	Adjusted odds ratio (95% CI)	p-value[a)]
Baseline *EGFR* mutation status				
19Del vs. others	2.15 (1.23-3.78)	0.008	2.14 (1.20-3.83)	0.010[b)]
PFS of first-line TKI				
> 11 mo vs. ≤ 11 mo	1.82 (1.05-3.18)	0.034	1.82 (1.02-3.25)	0.044[c)]
Rebiopsy site				
Metastasis vs. primary	2.17 (1.19-3.97)	0.012	1.97 (1.06-3.67)	0.032[d)]

Huang YH et al. *Cancer Res Treat*. 2018 Oct;50(4):1294-1303

Does the drug matter?



n=395
28 centers
Japan

Nosaki K et al. *Lung Cancer*. 2016 Nov;101:1-8.

Samsung Medical Center cohort

Table 3
Success rates of repeat biopsies, T790 M mutation rates, and histologic Transformation according to EGFR-TKIs.

	Afatinib	Erlotinib	Gefitinib	Total
Number of acquired resistance (A)	116	57	165	338
Number of repeat biopsies (B)	89	48	137	274
Rate of repeat biopsies (B/A)	76.7%	84.2%	83%	81.1%
Number of successful repeat biopsies (C)	86	44	133	263
Rate of successful repeat biopsies (C/A)	74.1%	77.2%	80.5%	77.8%
Number of T790 M mutation (D)	35	25	73	133
Rate of T790 M mutation (D/C)	40.7%	56.8%	54.9%	50.6%
Number of histologic transformations	5	0	1	6
Small cell carcinoma	2	0	1	3
Squamous cell carcinoma	3	0	0	3

2014/01 - 2016/12
First-line EGFR TKI

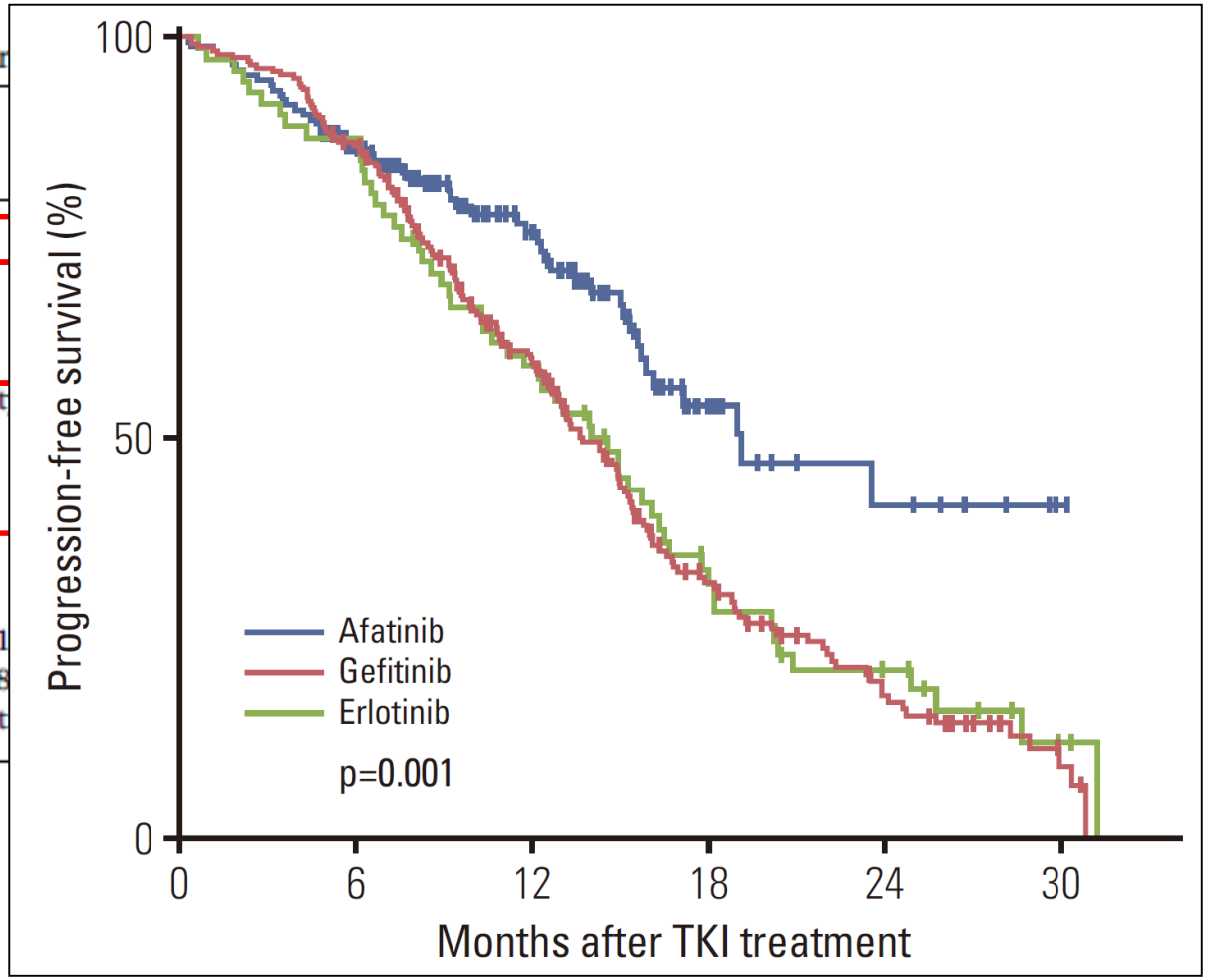
Afatinib vs Gefitinib or Erlotinib ($p = 0.026$)

- Multivariate analysis (EGFR-TKIs, baseline EGFR mutation types, and sex), for T790M mutation
  - Type of EGFR-TKI (afatinib vs. gefitinib or erlotinib)
    - Adjusted odds ratio [aOR], 0.45 (95%CI, 0.254 - 0.795); $p = 0.006$
  - Baseline EGFR mutation (deletion 19 vs. L858R)
    - aOR, 2.00 (95% CI, 1.167 - 3.430); $p = 0.012$

Lee K et al. *Lung Cancer*. 2019 Apr;130:87-92.

Samsung Medical Center cohort

Patient character
Median age
Sex, (%)
Male
Female
EGFR mutation t
Del 19
L858R
Uncommon
L861Q
G719X
G719X + L861
G719X + S768
Exon 20 insert



Lee K et al. *Lung Cancer*. 2019 Apr;130:87-92.
Kim Y et al. *Cancer Res Treat*. 2019 Apr;51(2):502-509.

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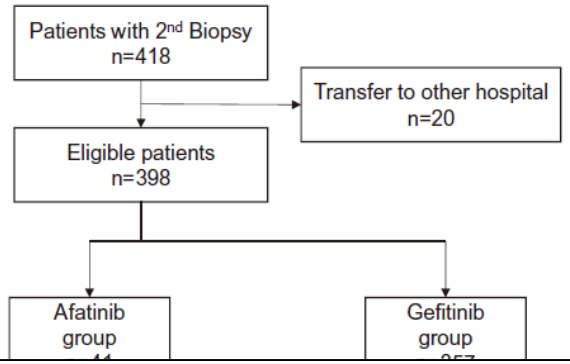
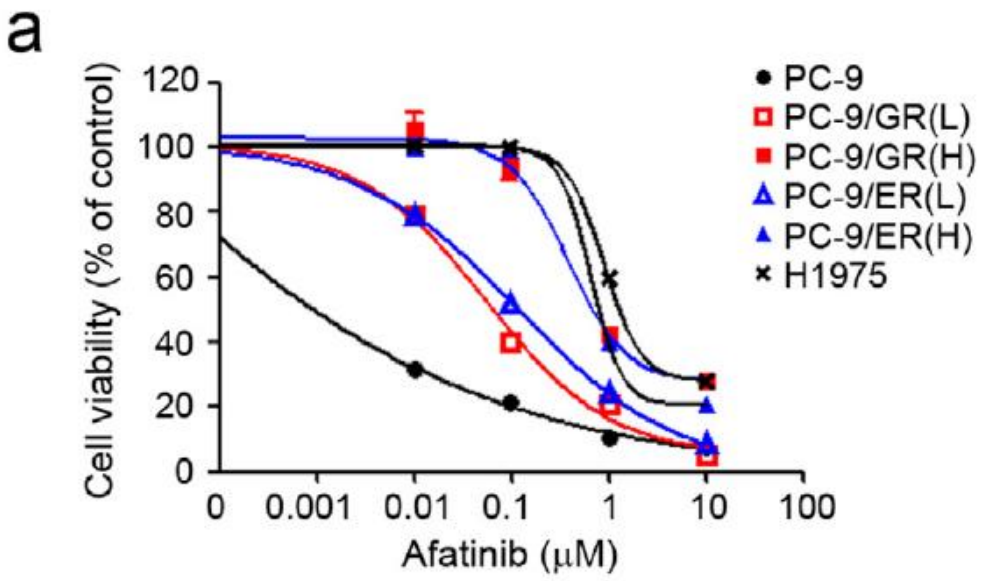
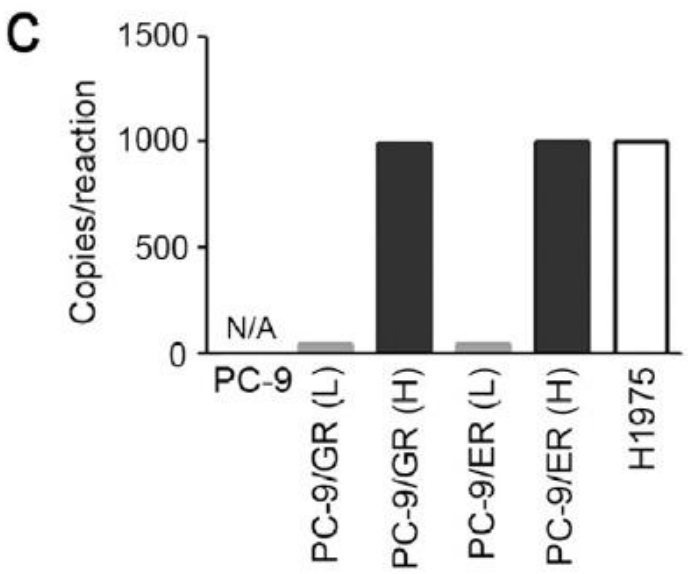
Comparison of T790M Acquisition Between Patients Treated with Afatinib and

Byung Woo Yoon*, Jae Hoon Kim†, Seung Hyeon Lee‡, Chang-Min Choi*, Jin Kyung Rho§, Shinkyo Yoon*, Dae Ho Lee*, Sang-We Kim*, Tae-Won Jang† and Jae Cheol Lee*



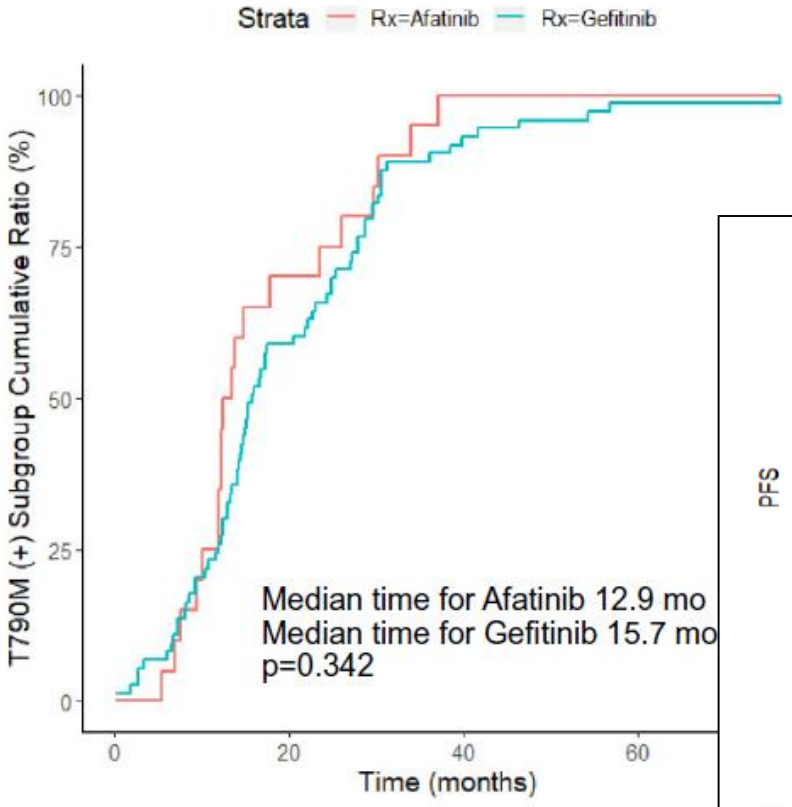




IIIB	7 (17.1%)	93 (25.1%)		7 (17.1%)	21 (17.1%)	
IVA	7 (17.1%)	95 (26.6%)		7 (17.1%)	20 (16.3%)	
IVB	27 (65.9%)	169 (47.3%)		27 (65.9%)	82 (66.7%)	
1st biopsy			.324			.506
EGFR mutations						
E19del	27 (65.9%)	212 (59.4%)		27 (65.9%)	88 (71.5%)	
L858R	11 (26.8%)	131 (36.7%)		11 (26.8%)	31 (25.2%)	
Others	3 (7.3%)	14 (3.9%)		3 (7.3%)	4 (3.3%)	
T790M (+)	20 (48.8%)	146 (40.9%)	.422	20 (48.8%)	73 (59.3%)	.317

Yoon BW et al. *Transl Oncol*. 2019 Jun;12(6):852-858.

a



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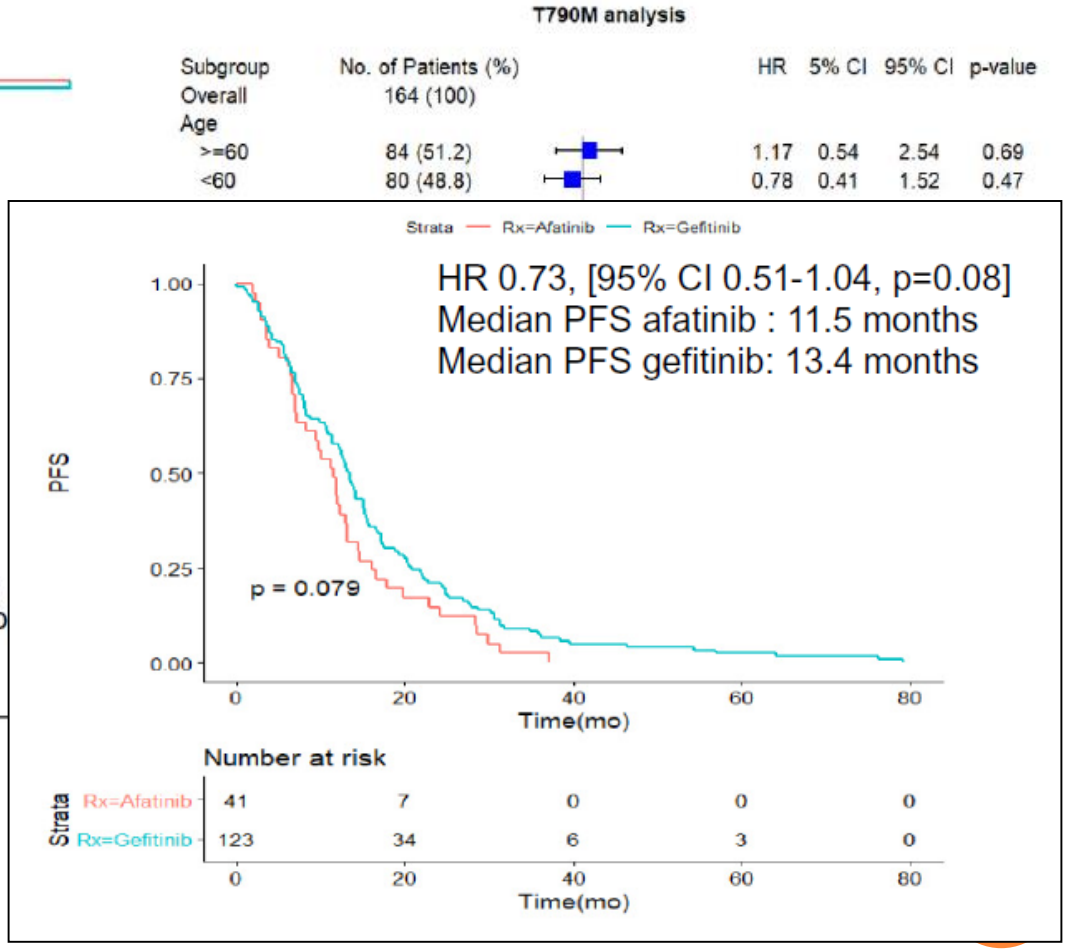
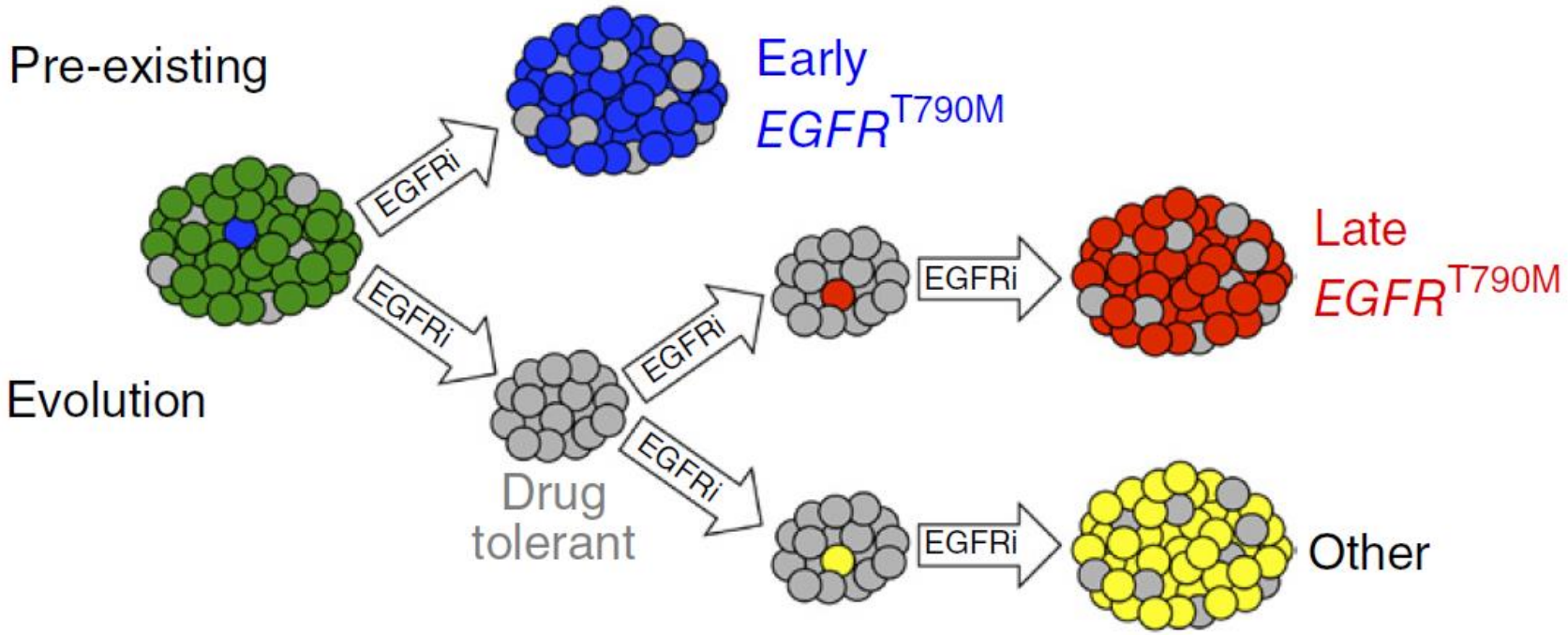


Yoon BW et al. *Transl Oncol*. 2019 Jun;12(6):852-858.

THE DEVELOPMENT OF SECONDARY T790M



Hata AN et al. *Nat Med*. 2016 Mar;22(3):262-9.

Factors reported to be associated with secondary T790M

- Factors favor secondary T790M
  - Longer EGFR TKI duration or PFS
  - EGFR exon 19 deletion
  - Gefitinib or 1st generation EGFR TKI
  - Male
  - Initial liver metastasis
- Factors against secondary T790M
  - Uncommon EGFR mutation

Take home messages

- The real world efficacy of EGFR TKIs reflects the results from RCTs.
  - Comparable PFS among the TKIs
  - Longer afatinib PFS for uncommon EGFR mutation
- Several factors associated with secondary T790M were reported.
  - EGFR TKI treatment duration
  - EGFR mutation type
  - EGFR TKI
  - Gender
  - Initial metastasis site

Thank you