Afatinib in patients with *EGFR* mutation-positive NSCLC harboring uncommon mutations: overview of clinical data

Yi-Long Wu,[1] Nobuyuki Yamamoto,[2] Chong-Jen Yu,[3]
Sai-Hong I Ou,[4] Angela Märten,[5] Caicun Zhou[6]

Presented by: Jin-Ji Yang[7]

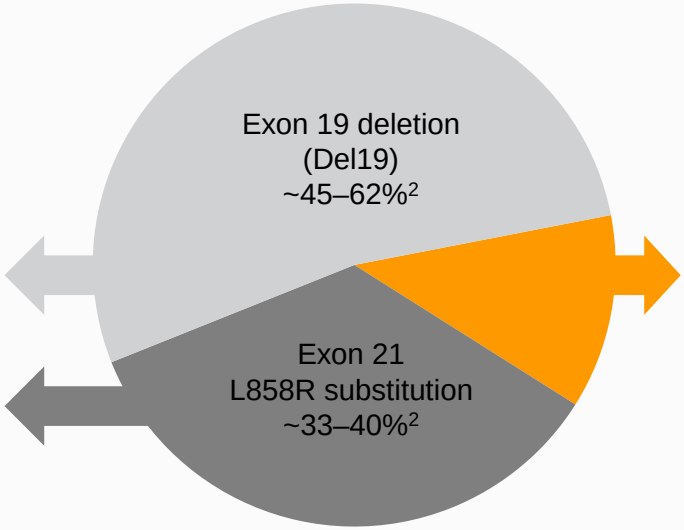
[1 1]Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China;
[2]Wakayama Medical University, Wakayama, Japan;
[3]National Taiwan University and National Taiwan University Hospital, Taipei City, Taiwan;
[4]University of California Irvine School of Medicine, Orange, CA, USA;
[5]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany;
[6]Shanghai Pulmonary Hospital, Shanghai, China;
[7]Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China

Introduction

- In patients with adenocarcinoma, the most common type of NSCLC, somatic mutations of *EGFR* have been reported in:

~50% of Asian patients;[1] 10–15% of Caucasian patients[1]

***EGFR* mutation type:**



The most frequent *EGFR* mutations in these populations are the Del19 and/or L858R mutations[3]

~10–15% of *EGFR*m+ tumors harbor uncommon *EGFR* mutations, comprising mutations in exons 18–21[3]

*EGFR*m+, *EGFR* mutation-positive.

1. Chan BA and Hughes GM. Transl Lung Cancer Res 2015;4(1):36–54;
2. Reguart N and Remon J. Future Oncol 2015;10(5):838–43;
3. Shen Y-C, et al. Lung Cancer 2017;110:56–62

Therapies for treatment of patients with *EGFR*m+ NSCLC

- EGFR TKIs are recommended for first-line treatment of patients with NSCLC with common *EGFR* mutations (Del19 or L858R):[1]
  - Reversible first-generation EGFR TKIs: **erlotinib**[2] and **gefitinib**[3]
  - Irreversible second-generation ErbB family blocker: **afatinib**[4*]
  - Irreversible third-generation EGFR/T790M inhibitor: **osimertinib**[5]
- Other EGFR TKIs are also being assessed in Phase III trials as first-line treatment options for patients with Del19/L858R *EGFR*m+ NSCLC:
  - Irreversible second-generation ErbB family blocker: **dacomitinib**[6]
- The optimal sequence of EGFR TKIs for the treatment of patients with NCSLC with common *EGFR* mutations is currently under debate

*Afatinib is indicated for first-line treatment of patients with NSCLC with non-resistant *EGFR* mutation.
TKI, tyrosine kinase inhibitor.
1. Novello S, et al. Ann Oncol 2016;27(Suppl. 5):v1–27; 2. U.S. FDA 2016. Tarceva. Highlights of prescribing information;
3. U.S. FDA 2015. Iressa. Highlights of prescribing information; 4. U.S. FDA 2018. Gilotrif. Highlights of prescribing information;
5. U.S. FDA 2018. Tagrisso. Highlights of prescribing information; 6. Wu Y-L, et al. Lancet Oncol 2017;18(11):1454–66

Trials of EGFR TKIs in the first-line treatment of patients with *EGFR*m+ NSCLC

- Patients with uncommon *EGFR* mutations were included in only some clinical trials of EGFR TKIs as first-line therapy:

	Erlotinib	Gefitinib	Afatinib	Osimertinib	Dacomitinib
Common (Del19/L858R) or uncommon *EGFR* mutations allowed		NEJ002[1]*, IPASS[2]†	LUX-Lung 2[3]‡, 3[4]‡ and 6[5]‡		
Common (Del19/L858R) *EGFR* mutation required	OPTIMAL[6], ENSURE[7]		LUX-Lung 7[8]	FLAURA[9]	ARCHER 1050[10]§

There is a paucity of data on the efficacy of most EGFR TKIs in patients with NSCLC harboring uncommon *EGFR* mutations

*5 patients with uncommon mutations received gefitinib[11]; †3 patients with uncommon mutations excluding T790M received gefitinib[2]; ‡*EGFR* mutation was required; §Patients with concomitant uncommon *EGFR* mutations, other than T790M, were excluded.

1. Maemondo M, et al. N Engl J Med 2010;362:2380–8; 2. Mok TS, et al. N Engl J Med 2009;361:947–57; 3. Yang JC, et al. Lancet Oncol 2012;13: 539–48; 4. Sequist LV, et al. J Clin Oncol 2013; 31(27):3327–34; 5. Wu Y-L, et al. Lancet Oncol 2014;15:213–22; 6. Zhou C, et al. Lancet Oncol 2011;12:735–42; 7. Wu Y-L, et al. Ann Oncol 2015;26:1883–89; 8. Park K, et al. Lancet Oncol 2016;17(5):577–89; 9. Soria JC, et al. N Engl J Med 2018;378(2):113–25; 10. Wu Y-L, et al. Lancet Oncol 2017;18(11):1454–66; 11. Watanabe S, et al. J Thoracic Oncol 2014;9:189–94

Pre-clinical activity against uncommon *EGFR* mutations

- Afatinib has shown similar *in vitro* activity against L861Q and S768I mutations as it has against L858R
  - Afatinib IC_{50} values were consistently low across the three cell lines evaluated[1]
  - Erlotinib and osimertinib IC_{50} values were higher and variable across the cell lines[1]

	Afatinib			Erlotinib			Osimertinib		
Mutation	L858R	L861Q	S768I	L858R	L861Q	S768I	L858R	L861Q	S768I
IC_{50}	0.2 nM	0.5 nM	0.7 nM	4.5 nM	92 nM	146 nM	2.5 nM	9 nM	49 nM

- Afatinib reduced cell proliferation and inhibited EGFR phosphorylation at similar concentrations in L858M/L861Q- and L858R-mutant cells[2]
  - First- and third-generation EGFR TKIs exhibited a decreased capacity to reduce cell proliferation and prevent EGFR phosphorylation in L858M/L861Q cells, compared with L858R-mutant cells[2]

IC_{50}, half maximal inhibitory concentration.

1. Banno E, et al. Cancer Sci 2016;107(8):1134–40;
2. Saxon JA, et al. J Thorac Oncol 2017;12(5):884–9

Combined analysis of clinical data from LUX-Lung 2, 3 and 6[1]

- 75 of 600* patients (13%) assigned to receive afatinib in the three trials had tumors harboring uncommon *EGFR* mutations
- Patients were grouped according to mutation status:

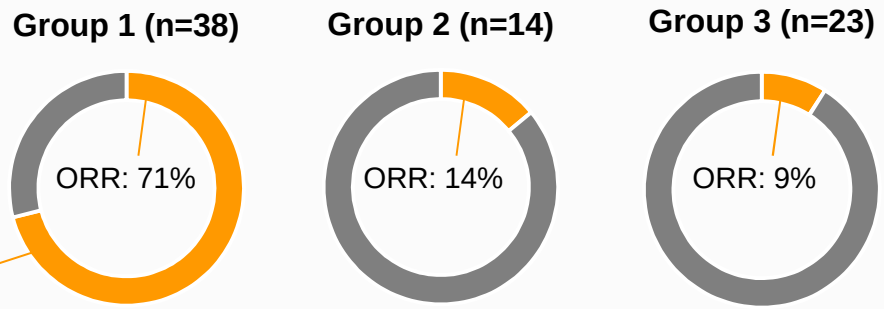
Group 1 Point mutations or duplications in exons 18–21, alone or in combination with each other

Group 2 *De novo* T790M mutation in exon 20, alone or in combination with other mutations

Group 3 Exon 20 insertions

ORR† by mutation type in Group 1:

S768I (n=8): 100%
G719X (n=18): 78%
L861Q (n=16): 56%



Median PFS (95% CI), months	10.7 (5.6–14.7)	2.9 (1.2–8.3)	2.7 (1.8–4.2)
Median OS (95% CI), months	19.4 (16.4–26.9)	14.9 (8.1–24.9)	9.2 (4.1–14.2)

*In LUX-Lung 3, an additional patient with wild-type EGFR was mistakenly assigned to afatinib; †Partial response + complete response.
CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression free survival.
1. Yang JC, et al. Lancet Oncol 2015;16(7):830–8

Phase IIIb open-label, single-arm study: interim analysis[1]*

Asian patients (N=479) received afatinib 40 mg (orally, once daily) until investigator-assessed tumor progression or lack of tolerability

Phase IIIb	Patients	Primary endpoint	Other endpoints
Open label, single arm, multicenter	Advanced *EGFR*m+ NSCLC; EGFR-TKI naïve; ECOG PS 0–2; Patients with asymptomatic brain metastases† were eligible	Safety	Time to symptomatic progression,‡ PFS

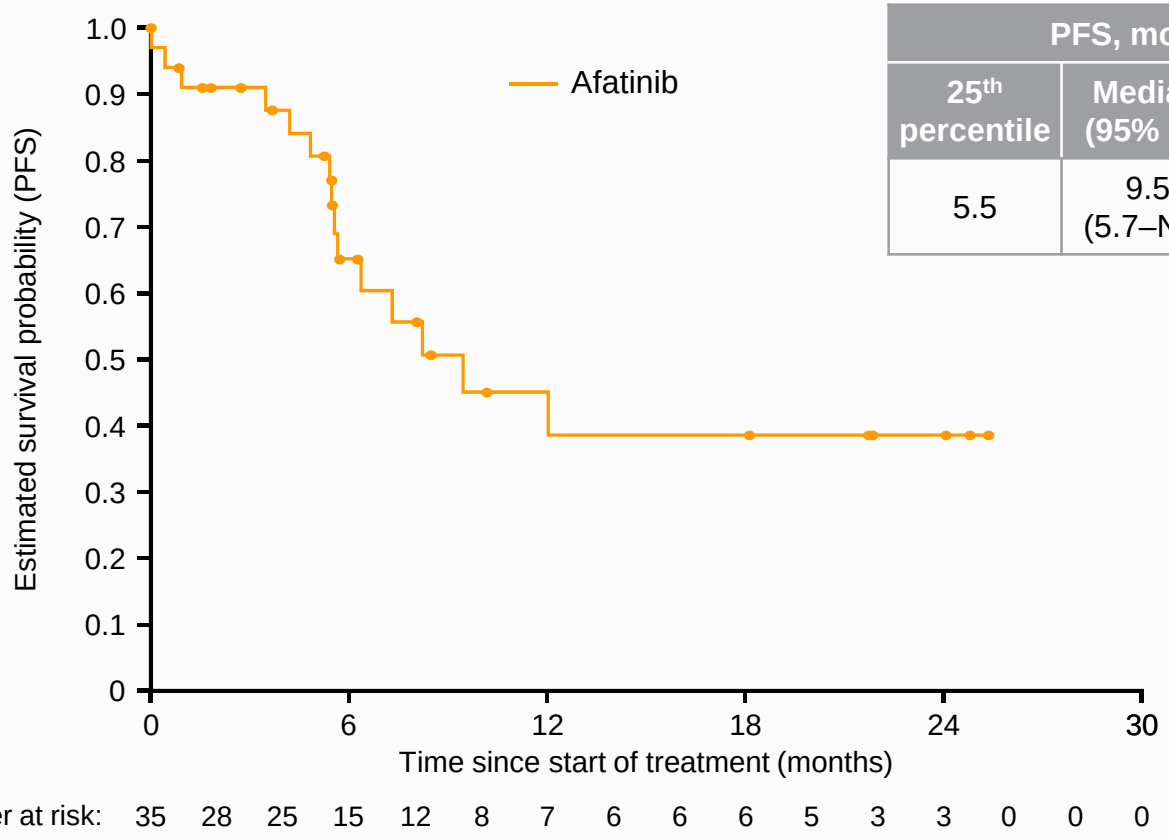
Mutation type	Patients, n (%)
*EGFR*m+	479 (100)
Uncommon *EGFR* mutations§	55 (11)
Exon 18–21 point mutations/duplications	35 (7)
Exon 20 insertions	18 (4)
Exon 20 insertions and T790M	1 (<1)
T790M	1 (<1)

*Data from larger Asian patient populations will be evaluated in further analyses of this trial; †For at least 4 weeks on stable doses of medication; ‡Time from first administration of afatinib to the date of first documented clinically significant symptomatic progression that required a change in or stopping of anti-cancer treatment, according to the investigator's assessment; §Patients with uncommon *EGFR* mutations only (not including patients with tumors harboring both common and uncommon *EGFR* mutations).

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

1. Wu Y-L, et al. WCLC 2017. Poster P3.01-036

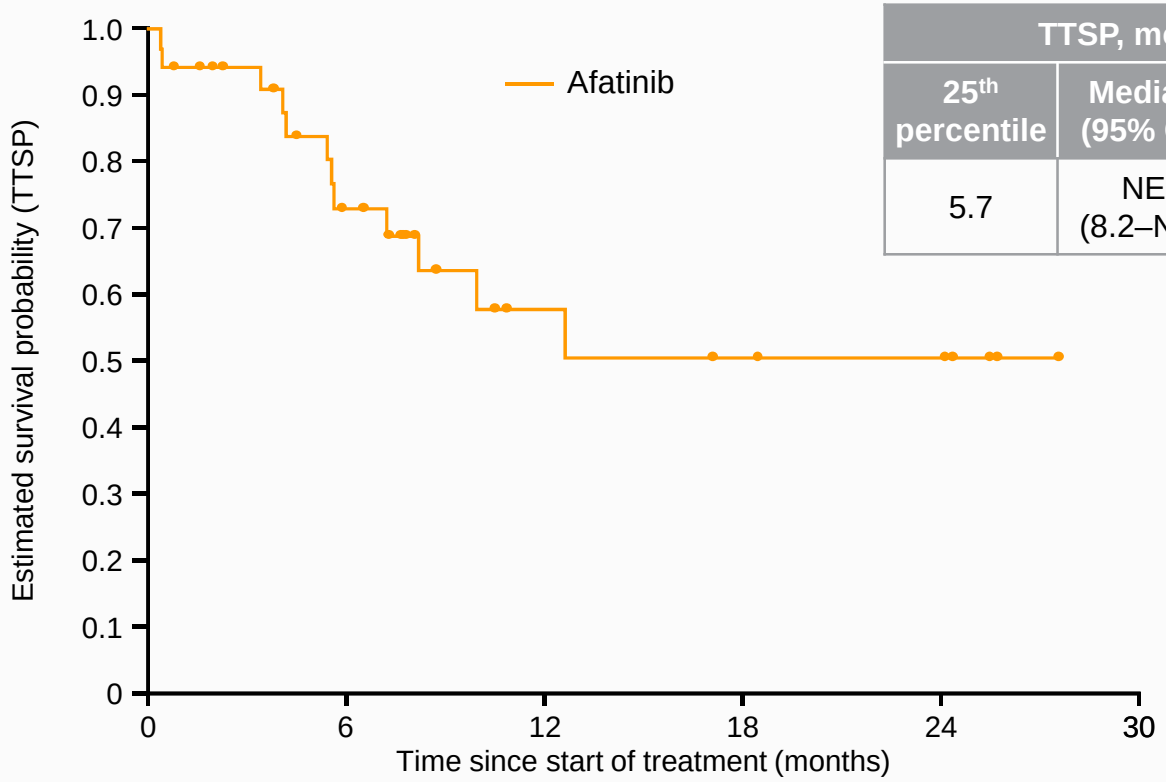
PFS in patients with tumors harboring point mutations (G719X, L861Q, S768I) or duplications in exons 18–21



PFS, months		
25th percentile	Median (95% CI)	75th percentile
5.5	9.5 (5.7–NE)	NE

NE, not evaluable.

Time to symptomatic progression in patients with tumors harboring point mutations (G719X, L861Q, S768I) or duplications in exons 18–21



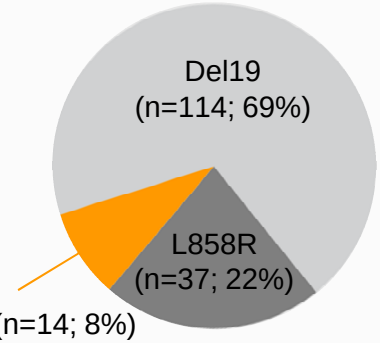
TTSP, months		
25th percentile	Median (95% CI)	75th percentile
5.7	NE (8.2–NE)	NE

TTSP, time to symptomatic progression.

Retrospective real-world analysis[1,2]

- 165 patients with recurrent/metastatic *EGFR*m+ NSCLC were treated with first-line afatinib at a single institute in South Korea[1]

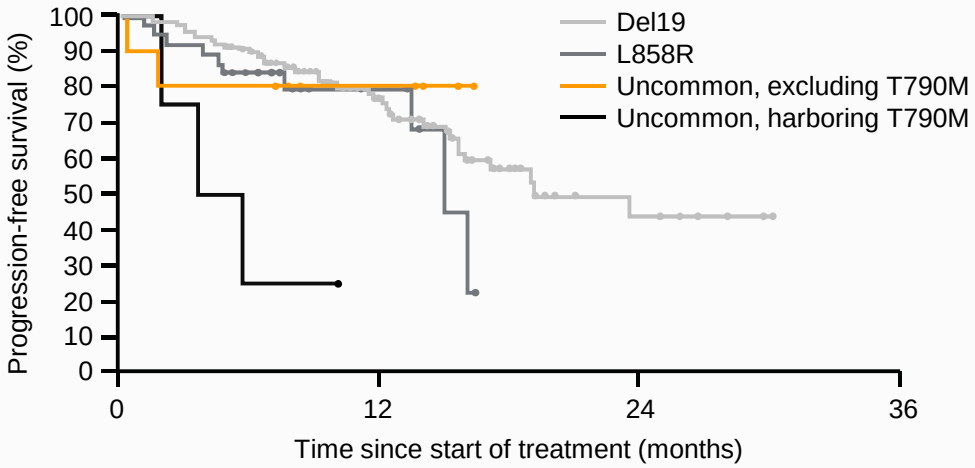
***EGFR* mutation type[1]**



Uncommon (n=14; 8%)

G719X (n=3)
G719X + S768I (n=1)
Del19 + L747_P753>Q (n=1)
Exon 20 insertion (n=1)
L861Q (n=3)
L858R + H870R (n=1)

Del19 + T790M (n=1)
L858R + T790M (n=3)



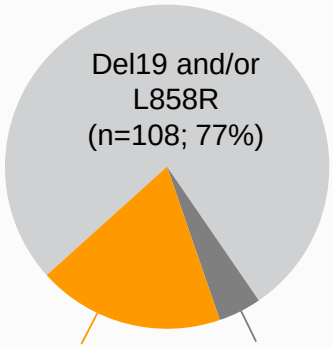
EGFR mutation type	Median PFS, months[2]		ORR[1]
Uncommon, excluding T790M (n=10)	NR*	p=0.01	80%
Uncommon harboring T790M (n=4)	4.7		25%
Common, Del19 (n=114)	19.1		-
Common, L858R (n=37)	15.8		-

*Median follow-up time was 17.7 months (95% CI: 16.2–18.9 months).
NR, not reached.
1. Kim Y, et al. WCLC 2017. Poster P3.01-023; 2. Kim Y, et al. J Thorac Oncol 2017;12(Suppl. 2):S2209

Retrospective real-world analysis[1]

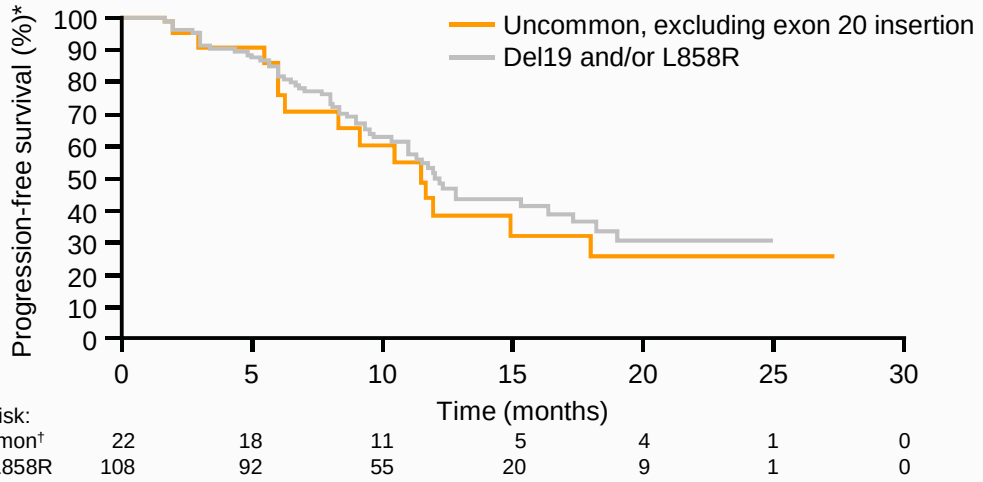
- 140 patients with *EGFR*m+ NSCLC were treated with first-line afatinib at a single institute in Taiwan

***EGFR* mutation type[1]**



Uncommon (n=26; 19%)
- G719A (n=6)
- L861Q (n=10)
- Exon 20 insertion (n=4)
- G719A + E709L (n=1)
- G719A + S768I (n=1)
- G719A + T790M (n=1)
- G719S + L747S (n=1)
- L861R + R776G (n=1)
- L861Q + S768I (n=1)

Complex mutation with Del19 or L858R (n=6; 4%)



EGFR mutation type	Median PFS, months[1]	ORR[1]
Uncommon (n=26)	9.2	54%
Uncommon, excluding exon 20 insertion (n=22)	11.5	59%
Common, Del19 and/or L858R (n=108)	12.2	70%
Complex with Del19/L858R (n=6)	9.2	67%

*Adapted from Liang. Oncotarget 2017 under the terms of the Creative Commons Attribution License 3.0 (CC BY 3.0).
† Uncommon *EGFR* mutations, excluding exon 20 insertion
1. Liang S-K, et al. Oncotarget 2017;8(52):90430–43

Summary

- Afatinib has pre-clinical and clinical activity in patients with NSCLC harboring certain uncommon *EGFR* mutations
- ORR, PFS and OS outcomes from a post-hoc analysis of LUX-Lung 2, 3 and 6 showed that afatinib was more active in patients with tumors harboring point mutations or duplications in exons 18–21, compared with *de novo* T790M mutations or exon 20 insertions[1]
- The activity of afatinib against certain uncommon *EGFR* mutations is being substantiated by studies outside of the randomized controlled trial setting,[2] including in real-world clinical practice, generally demonstrating high ORR and long PFS[3–5]

1. Yang JC, et al. Lancet Oncol 2015;16(7):830–8; 2. Wu Y-L, et al. WCLC 2017. Poster P3.01-036;
3. Kim Y, et al. WCLC 2017. Poster P3.01-023; 4. Kim Y, et al. J Thorac Oncol 2017;12(Suppl. 2):S2209;
5. Liang S-K, et al. Oncotarget 2017;8(52):90430–43

Acknowledgments

- We thank all patients and their families, and investigators and staff at all clinical sites, for their valuable participation in these studies
- LUX-Lung 2, 3 and 6 were funded by Boehringer Ingelheim
- Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Victoria Steele of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this oral presentation
- Previously presented: Märten A, et al. ELCC 2018; poster #158P

Online resources

Scan the QR code for an electronic copy of the slides and supplementary content*