Treatment Options for NSCLC Patients With Uncommon Mutations

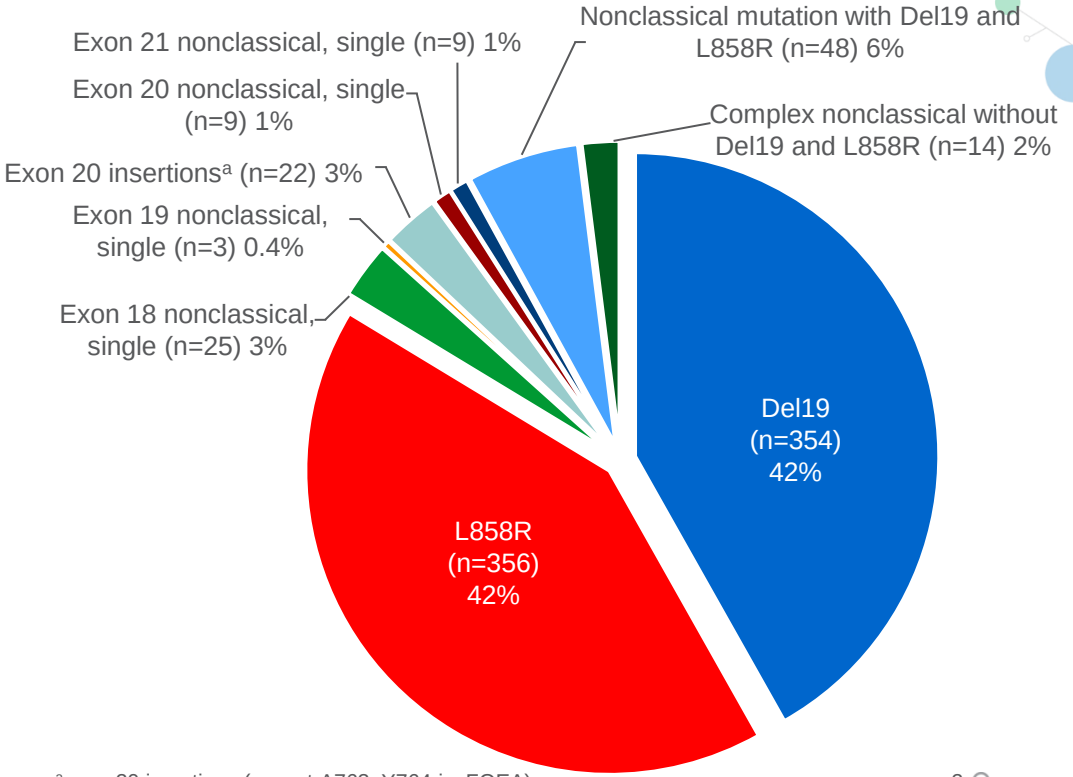
Jin-Seok Ahn, MD, PhD

Samsung Medical Center, Sungkyunkwan University

Seoul, Korea

Uncommon *EGFR* Mutations in NSCLC

- In stage IIIB-IV NSCLC, common *EGFR* mutations (L858R and Del19) account for ≈84% of all mutations
- **Uncommon mutations occur in ≈16% of *EGFR* mutation–positive NSCLC cases**
  - Exon 20 insertions (9%)
  - Uncommon mutations with Del19 or L858R complex mutations (30%)
  - Uncommon mutation alone or in combination with other uncommon mutations (61%)

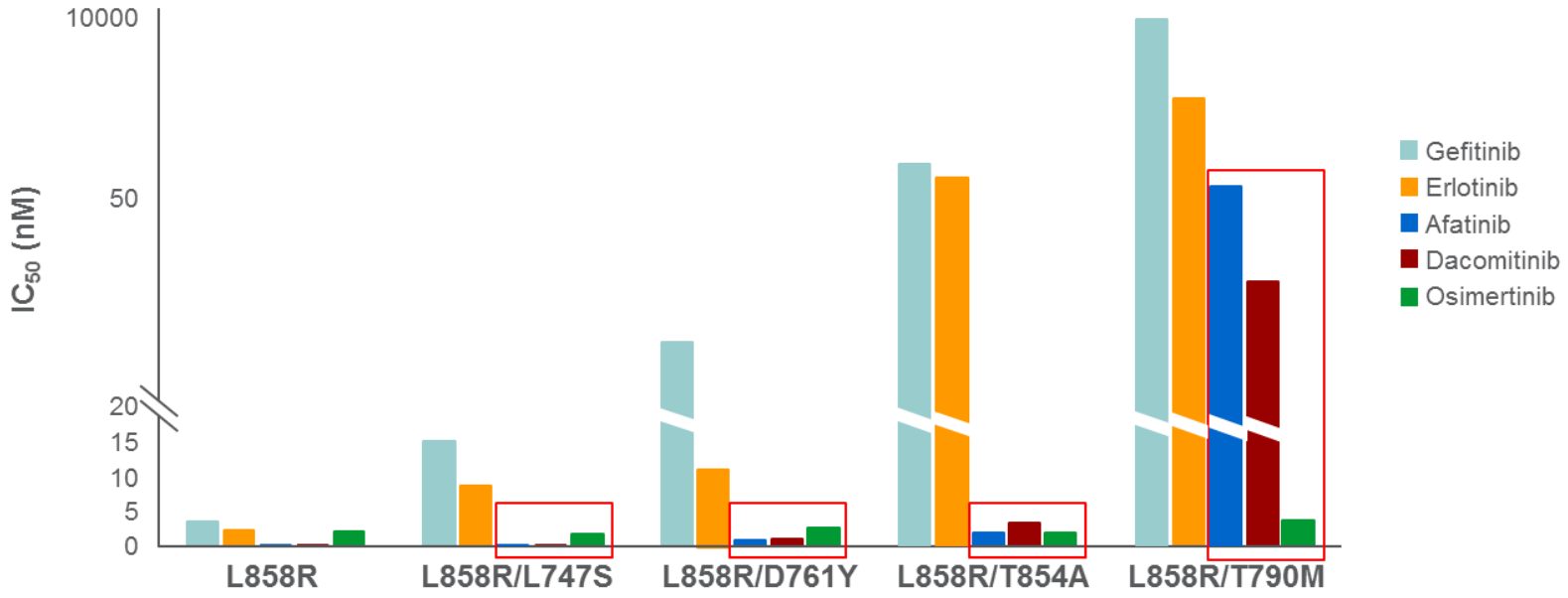


EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer. [a]exon 20 insertions (except A763_Y764 insFQEA)

Shen et al. *Lung Cancer*. 2017;110:56.

In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon *EGFR* Mutations

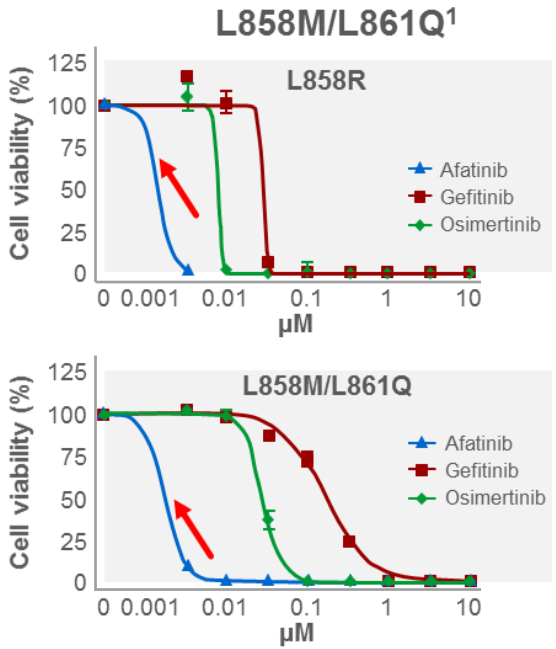
- Irreversible second- and third-generation TKIs overcome resistance induced by uncommon secondary mutations

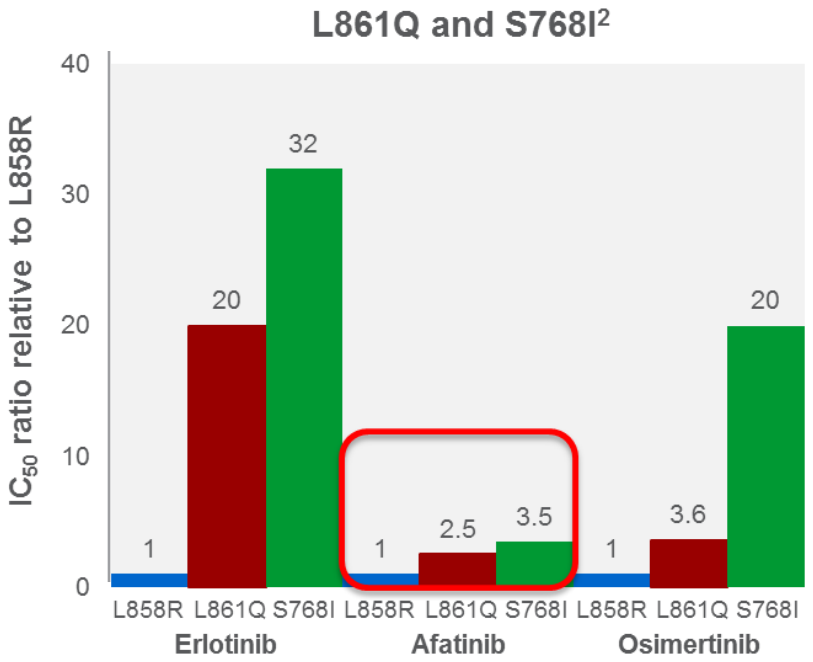


Chiba et al. *BMC Cancer*. 2017;17:281.

In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon *EGFR* Mutations

- In separate assays, first- and third-generation TKIs demonstrated reduced activity in cell lines harbouring uncommon mutations, whereas the response to afatinib was similar across cell lines



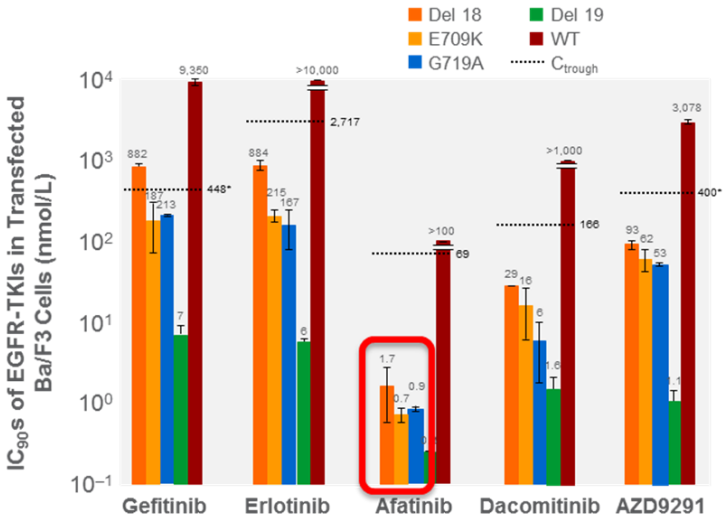


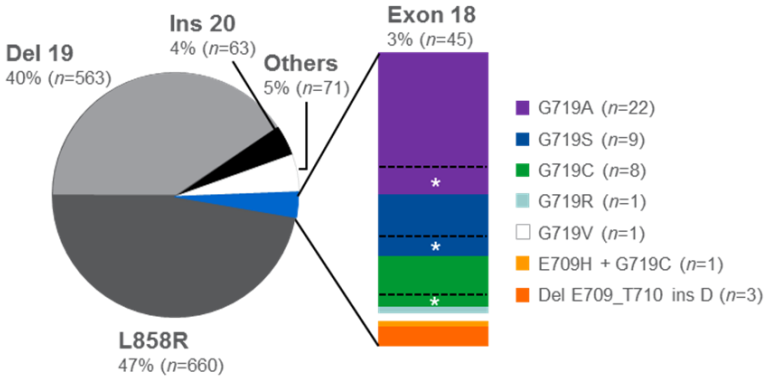
TKI = tyrosine kinase inhibitor; IC50 = 50% inhibitory concentration.

1. Saxon et al. *J Thorac Oncol*. 2017;12:884; 2. Banno et al. *Cancer Sci*. 2016;107:1134.

Molecular Predictors of Augmented Sensitivity to Afatinib Compared With First- or Third-Generation TKIs

- Mutational status of lung cancers treated between 2001 and 2015 were reviewed
- Of 1,402 mutations, Del19, L858R, and Ins20 were detected in 40%, 47%, and 4% of patients, respectively
- Exon 18 mutations, including G719X, E709X, and Del18, were detected in 3.2%
- In vitro assays demonstrated that afatinib had greater sensitivity to Exon 18 mutations than first- and third-generation TKIs

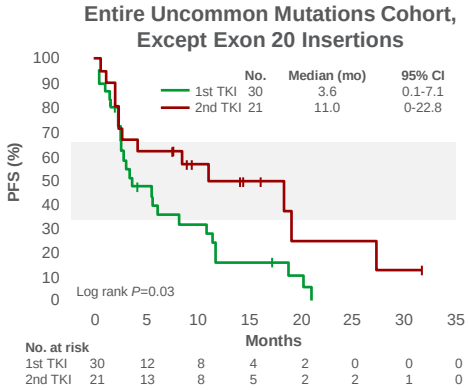


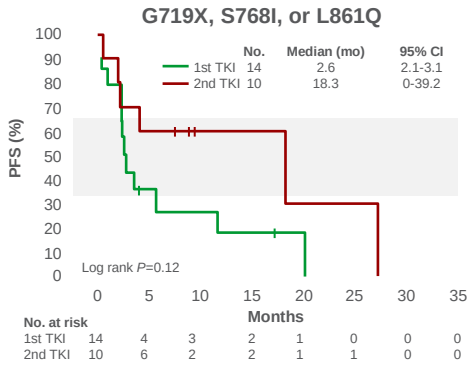


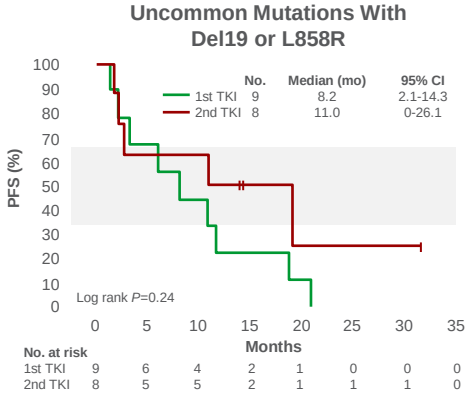
Kobayashi et al. *Clin Cancer Res.* 2015;21:5305.

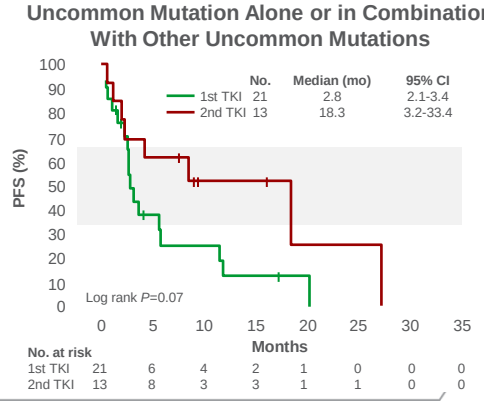
First-line Clinical Data: Retrospective Analysis of PFS in 57 Patients Treated With Afatinib or First-Generation TKIs

- In all mutation groups analysed, the afatinib group exhibited longer median PFS compared with first-generation TKIs
  - Entire uncommon mutations cohort, except exon 20 insertions[a]: 11.0 mo vs 3.6 mo
  - G719X, S768I, or L861Q: 18.3 mo vs 2.6 mo
  - Uncommon mutations with Del19 or L858R: 11.0 mo vs 8.2 mo
  - Uncommon mutation alone or in combination with other uncommon mutations: 18.3 mo vs 2.8 mo









CI = confidence interval. [a]exon 20 insertions (except A763_Y764 insFQEA).

Shen et al. *Lung Cancer*. 2017;110:56.

First-line Clinical Data: Prospective Efficacy Assessments in the LUX-Lung Programme

- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations[1-4]
- Of 600 patients given afatinib in LUX-Lung 2/3/6, 75 (13%) patients had uncommon *EGFR* mutations[1]

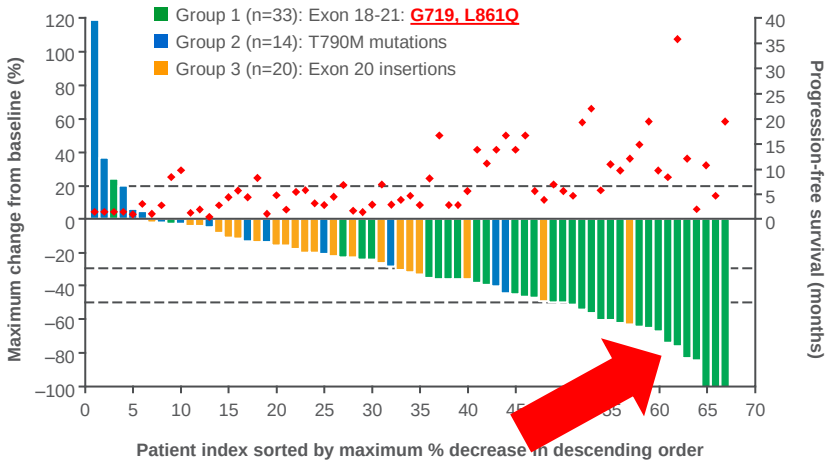
	LUX-Lung 2 Phase 2 (N=129)[5]	LUX-Lung 3 Phase 3 (N=345)[6]	LUX-Lung 6 Phase 3 (N=364)[4]
Treatment	Afatinib	Afatinib vs Cis/Pem	Afatinib vs Cis/Gem
Line of treatment	First- and second-line (after chemotherapy)	First-line	First-line
Mutation test	Direct sequ. (central)	EGFR29[a] (central)	EGFR29[a] (central)
Common mutations	Del19=52 L858R=54	Del19=170 L858R=138	Del19=186 L858R=138
Uncommon mutations; treated with afatinib[4]	N=23 N=23	N=37 N=26	N=40 N=26

[a]EGFR mutations detected by TheraScreen EGFR29 test. Common: 19 deletions in exon 19 and L858R in exon 21; Uncommon: 3 insertions in exon 20, L861Q, T790M, G719S, G719A and G719C, and S768I.

1. Yang et al. *Lancet Oncol*. 2015;16:830; 2. Passaro et al. *J Thorac Dis*. 2013;5:383; 3. Katakami et al. *J Clin Oncol*. 2013;31:3335; 4. Wu et al. *Lancet Oncol*. 2014;15:213; 5. Yang et al. *Lancet Oncol*. 2012;13:539; 6. Sequist et el. *J Clin Oncol*. 2013;31:3327.

LUX-Lung 2, 3, and 6: Efficacy of Afatinib in Patients With Uncommon Mutations (by Independent Review)

- 3 patients with point mutations or duplications in exons 18-21 achieved complete response (1 each with G719X, K739_1744dup6, and L858R+Q709G/V)



	T790M (n=14)	Exon 20 ins (n=23)	Mut/dup exon 18-21 (n=38)	G719X (n=18)	L861Q (n=16)	S768I (n=8)
Response rate (%)	14.3	8.7	71.1	77.8	56.3	100.0
PFS (months)	2.9	2.7	10.7	13.8	8.2	14.7
OS (months)	14.9	9.2	19.4	26.9	17.1	NE

Note: A patient may be presented in more than 1 category.

OS = overall survival; PFS = progression-free survival.

Yang et al. *Lancet Oncol*. 2015;16:830.

Responses* in Patients With NSCLC Harbouring Non-Resistant EGFR Mutations From LUX-Lung 2, 3, and 6

- Among the 75 afatinib-treated patients with uncommon *EGFR* mutations, 32 patients had a non-resistant *EGFR* mutation (G719X, L861Q, and/or S768I)

EGFR Mutation	Number of Afatinib-Treated Patients (n=32)	Number of Confirmed Responses (n=21)	Duration of Response (months) (n=21)
S768I	1	1	37.3
S768I and G719X	5	4	4.1, 13.2, 15.2, 29.5+
S768I and L858R	2	1	34.5+
G719X	8	6	5.7+, 8.1, 9.6, 23.5+, 25.2, 31.8+
G719X and L861Q	3	2	2.8+, 6.8
L861Q	12	7	2.8, 4.0, 4.1, 8.3+, 12.9, 15.2, 20.6
L861Q and del19	1	0	NA

IRC = independent review committee; NA = not applicable.
*IRC-accessed; + response ongoing at time of censoring.

GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.

Clinical Data in TKI-Pretreated Patients: Time to Treatment Failure With Afatinib

- 66 uncommon mutations were reported (18.4% of all known *EGFR* mutations in the compassionate-use programme)
  - Majority of patients (67%) received afatinib as third- or fourth-line treatment, with median treatment duration of 3.6 months
- No significant difference between median TTF for patients with uncommon/non-classical mutations (3.6 months) compared with those with Del19 (4.6 months) or L858R (5.8 months) mutations

Heigener et al. *Oncologist*. 2015;20:1167.

Clinical Data in TKI-Pretreated Patients: Best Response in Patients With LMD Harbouring Uncommon Mutations

- 3/11 patients with leptomeningeal carcinoma treated with afatinib harboured an uncommon Exon 18 mutation (G719X)
- Median CSF concentration in all 11 patients was 2.88 nM (afatinib's **IC_{50} for EGFR being 0.5 nM**). PFS and OS in patients harbouring a G719X mutation were 5.6 months (2.0-10.0) and 7.0 months (5.6 ongoing to 13.0)

Concentration of Afatinib in Plasma and CSF, Penetration Rate, and Efficacy in Patients With G719X-Positive NSCLC With LMD

	Concentration (nM)				
	Plasma	CSF	Best Response	PFS (Days)	OS (Days)
1	146.9	NE	PR	309	396
2	192.0	6.0	PD	61	212
3	767.6	0.8	PR	171[a]	171[b]

[a]Treatment continued after data cutoff; [b]Censored at data cutoff (patient still alive).
LMD = leptomeningeal disease; CSF = cerebrospinal fluid; PFS = progression-free survival; OS = overall survival; NE = not evaluated; PR = partial response; PD = progressive disease.

Tamiya et al. *Anticancer Res*. 2017;37:4177.

Real-World Experience With Afatinib in Patients With Uncommon Mutations: Pooled Analysis

Asian Phase 3b[1]

- **Patient Population:** EGFR TKI–naive patients from China, Hong Kong, India, Singapore, and Taiwan (N=479) with locally advanced/metastatic *EGFRm*+ NSCLC
- **Treatment:** afatinib 40 mg/d until investigator-assessed progression or lack of tolerability
- **Primary endpoint:** number of patients with serious AEs
- **Secondary endpoints**: TTSP, PFS, TRAEs

German NIS (GIDEON)[2]

- **Patient Population:** EGFR TKI–naive patients with locally advanced/metastatic *EGFRm*+ NSCLC (N=156)
- **Treatment:** afatinib 50, 40, 30, or 20 mg
- **Primary endpoint:** PFS at 1 year

Baseline Characteristics of Combined Trial Subgroups With Uncommon Mutations (N=54)[3]

	n (%)
Female	22 (40.7)
Age, y, median (range)	63.5 (35-79)
ECOG 0/1	50 (92.5)
ECOG 2	3 (5.6)
L861Q	13 (24.1)
S768I	3 (5.6)
G719X	23 (42.6)
Complex mutations[a]	21 (38.9)
Other mutations[b]	7 (13.0)

[a]11 patients with G719S/G719A/G719C; 3 patients with S768I/G719S/G719A/G719C; 2 patients with L861Q/G719S/G719A/G719C; 1 patient with S768I/L861Q/G719S/G719A/G719C; 1 patient each with G719A/L747V; L858A/T854A; del exon 18/ins exon20; delins exon20/delins exon20.
[b]2 exon 21 (non L857R), 1 exon 18, 1 exon 18: S695I, 1 del exon 18/ins exon20, 1 exon 19 point mutation/Kras exon 9; 1 G719A/L747V; 1 L858A/T854A.
AE = adverse event; TTSP = time to symptomatic progression; TRAE = treatment-related adverse event; ECOG = Eastern Cooperative Oncology Group.

1. Wu et al. WCLC 2018. Abstract P1.01-98; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02047903. Accessed October 16, 2018; 3. Boehringer Ingelheim. Data on file.

Real-World Experience With Afatinib *(cont'd)*: Best Response by Uncommon Mutation Type

L861Q, S768I, G719X	N (%)
CR	2 (5.9)
PR	18 (52.9)
SD	11 (32.4)
PD	3 (8.8)
ORR	20 (58.8)
DCR	31 (91.2)

L861Q	N (%)
CR	0 (0.0)
PR	4 (57.1)
SD	3 (42.9)
PD	0 (0.0)
ORR	4 (57.1)
DCR	7 (100.0)

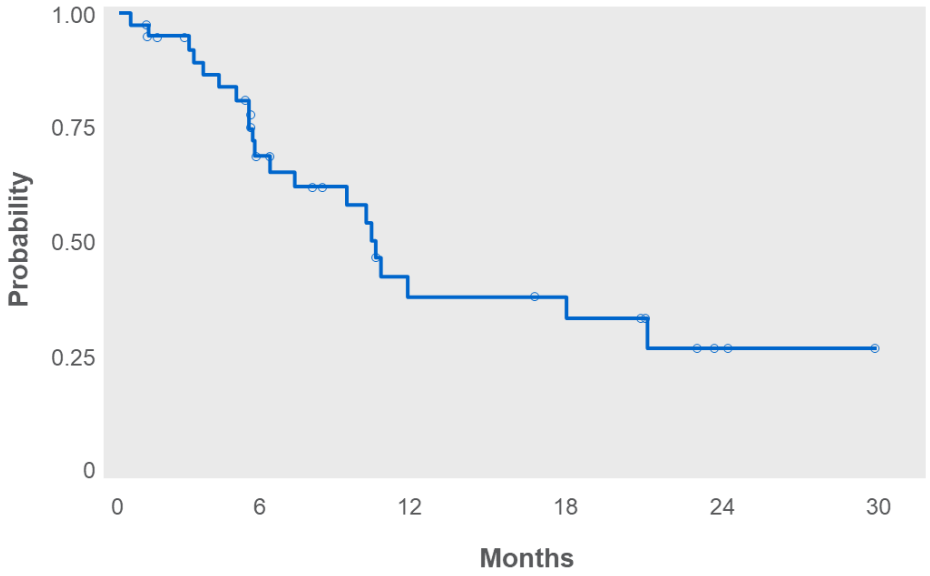
G719X	N (%)
CR	1 (5.3)
PR	10 (52.6)
SD	6 (31.6)
PD	2 (10.5)
ORR	11 (57.9)
DCR	17 (89.5)

Complex mutations[a]	N (%)
CR	0 (0.0)
PR	9 (47.4)
SD	8 (42.1)
PD	2 (10.5)
ORR	9 (47.4)
DCR	17 (89.5)

[a]11 patients DCR 17 (89.5) '19C; 2 | DCR 17 (89.5)
S768I/L861Q/G719S/G719A/G719C; 1 patient each with G719A/L747V; L858A/T854A; del exon 18/ins exon20; delins exon20/delins exon20.
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = overall response rate; DCR = disease control rate.

Boehringer Ingelheim. Data on file.

Real-World Experience With Afatinib *(cont'd)*: Time on Treatment



Mutation	N	Median Time (mo)
L861Q, S768I, G719X	40	10.7
L861Q	9	10.7
G719X	22	10.6
Complex mutations[a]	20	7.3

[a]11 patients with: G719S/G719A/G719C; 3 patients with: S768I/G719S/G719A/G719C; 2 patients with: L861Q/G719S/G719A/G719C; 1 patient with S768I/L861Q/G719S/G719A/G719C; 1 patient each with: G719A/L747V; L858A/T854A; del exon 18/ins exon20; delins exon20/delins exon20.

Boehringer Ingelheim. Data on file.

Osimertinib and Uncommon Mutations: Data From an Open-label, Multicentre, Phase II Single-Arm Trial

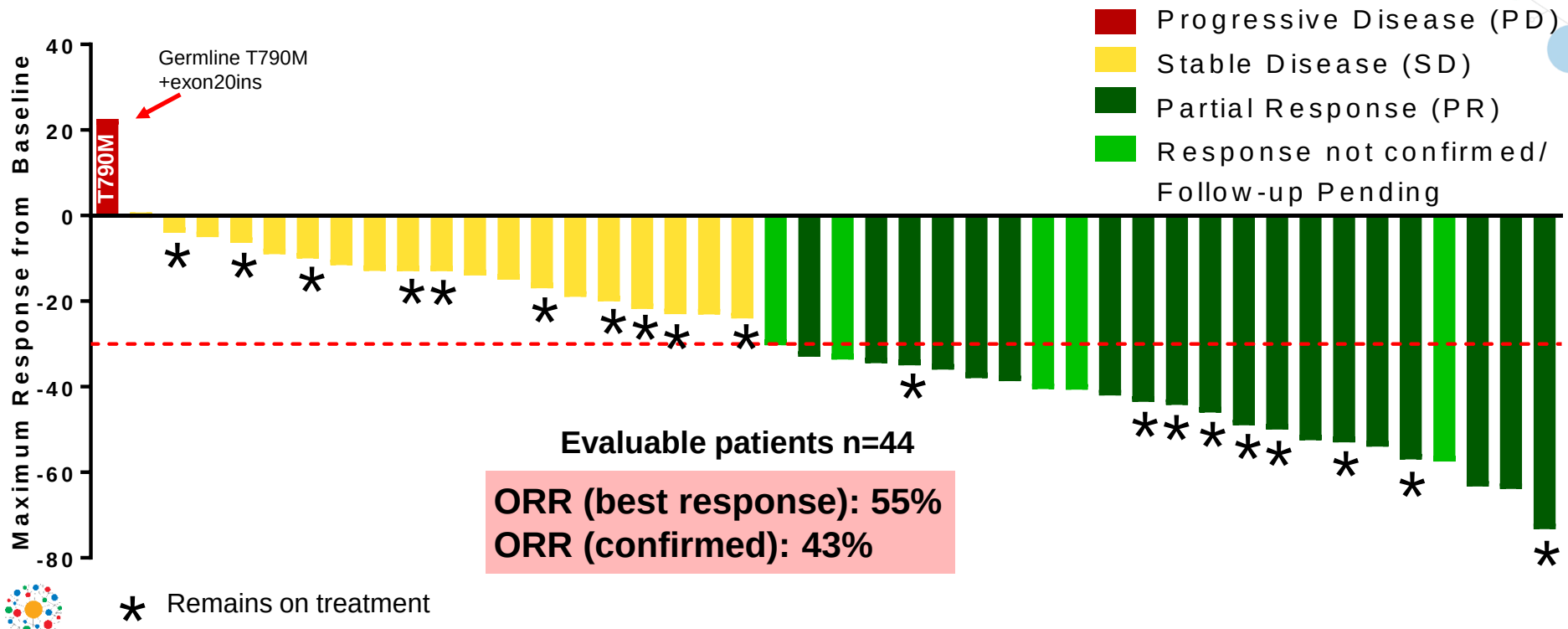
Response according to most frequent uncommon mutations

Mutation		Objective response, % (n, 95%CI)	Disease control rate, % (n, 95%CI)	6-month PFS (%, 95% CI)
G719A/C/D/S/X (n=19)	G719A/C/D/S/X (n=15) G719A/C/D/S/X + S768I (n=2) G719A/C/D/S/X + L861Q (n=2)	57.9 (10, 27.9-77.4)	89.5 (17, 74.3-100.0)	73.7 (69.2-78.2)
S768I (n=8)	S768I (n=6) S768I + G719A/C/D/S/X (n=2)	37.5 (3, 0.0-80.8)	87.5 (7, 57.9-100.0)	62.5 (50.7-74.4)
L861Q (n=9)	L861Q (n=7) L861Q + G719A/C/D/S/X (n=2)	77.8 (7, 43.9-100.0)	100 (9)	66.7 (56.4-77.0)

Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

Cho et al. WCLC 2018. Abstract OA10.05.

Poziotinib for EGFR and HER2 Exon 20 Mutant NSCLC: Phase II Trial Data



Heymach et al. WCLC 2018. Abstract OA02.06.

Summary

- Anecdotal data with erlotinib/gefitinib show variable and mainly limited responses to these EGFR TKIs in patients with NSCLC harbouring uncommon mutations
- In preclinical and clinical trials, afatinib has shown activity in TKI-naive and TKI-pretreated patients with NSCLC harbouring uncommon *EGFR* mutations
- Activity of afatinib against uncommon *EGFR* mutations in patients with LMD was also reported in a multicenter prospective study
- Clinical trial data show that afatinib was especially active in NSCLC tumours harbouring point mutations or duplications in exons 18-21 (eg, G719X, S768I, L861Q K739_1744dup6, and L858R+Q709G/V)
- Data in real-world studies with afatinib are in line with analyses from LUX-Lung trials
- Other inhibitors have recently reported Phase II data on activity in NSCLC with uncommon *EFGR* mutations