Efficacy of EGFR TKIs in Patients With NSCLC With Uncommon *EGFR* Mutations

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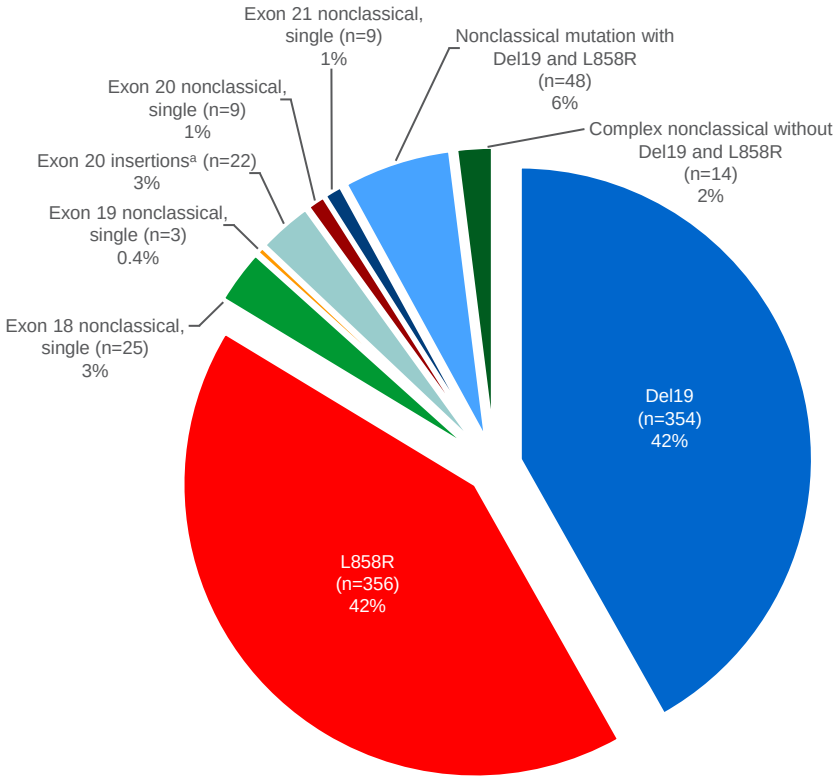
Disclosures

- Boehringer Ingelheim, AstraZeneca, Merck, Roche/Genentech

EGFR Mutations in NSCLC

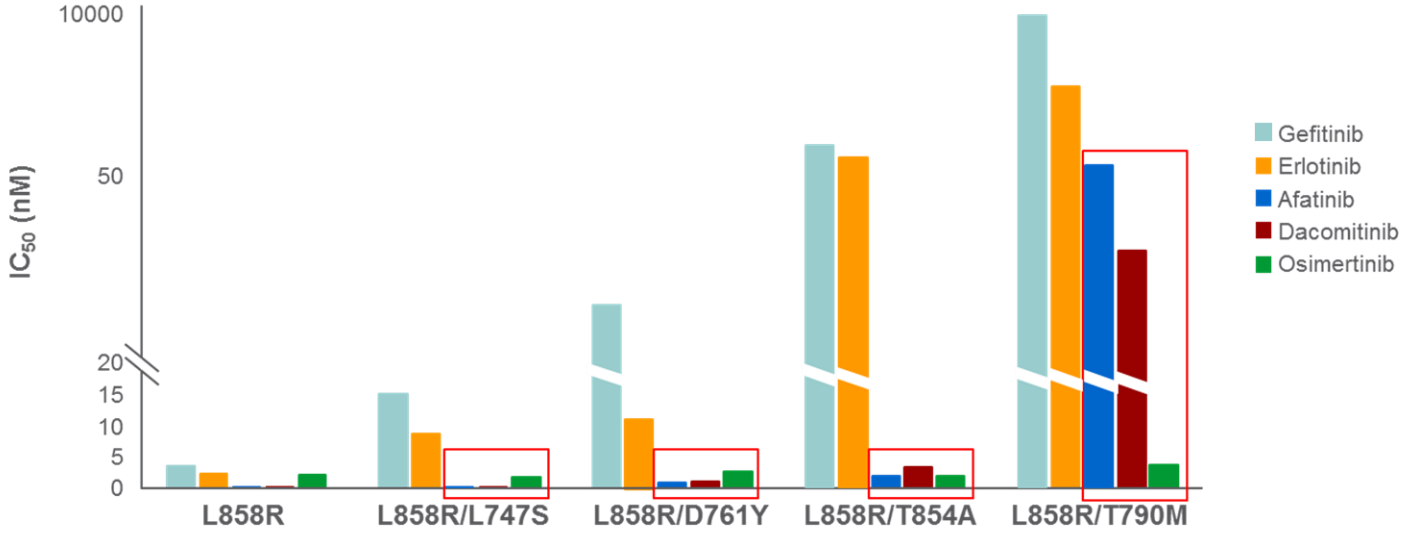
- The presence of somatic mutations in *EGFR* influences treatment strategy for patients with NSCLC
- In stage IIIB-IV NSCLC, common *EGFR* mutations (Del19 and L858R) account for ≈84% of all mutations
- Uncommon mutations occur in ≈16% of *EGFR* mutation–positive NSCLC cases
  - Exon 20 insertions (9%)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



Shen et al. *Lung Cancer*. 2017;110:56.
[a] Exon 20 insertions (except A763_Y764 insFQEA).
EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer.

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

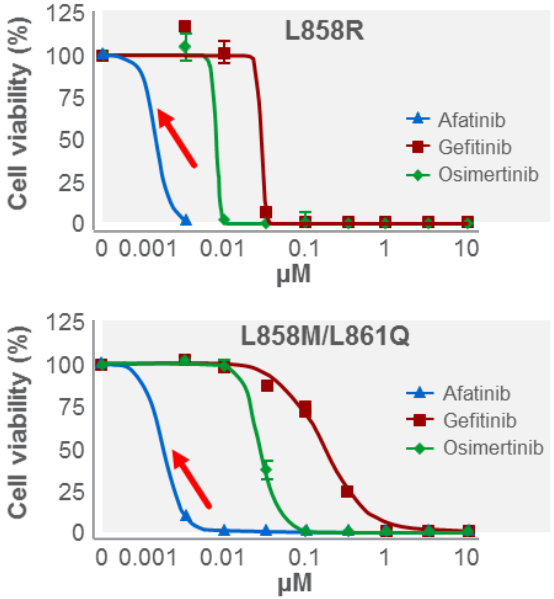


TKI = tyrosine kinase inhibitor; IC_{50} = half-maximal inhibitory concentration.
Chiba et al. *BMC Cancer*. 2017;17:281.

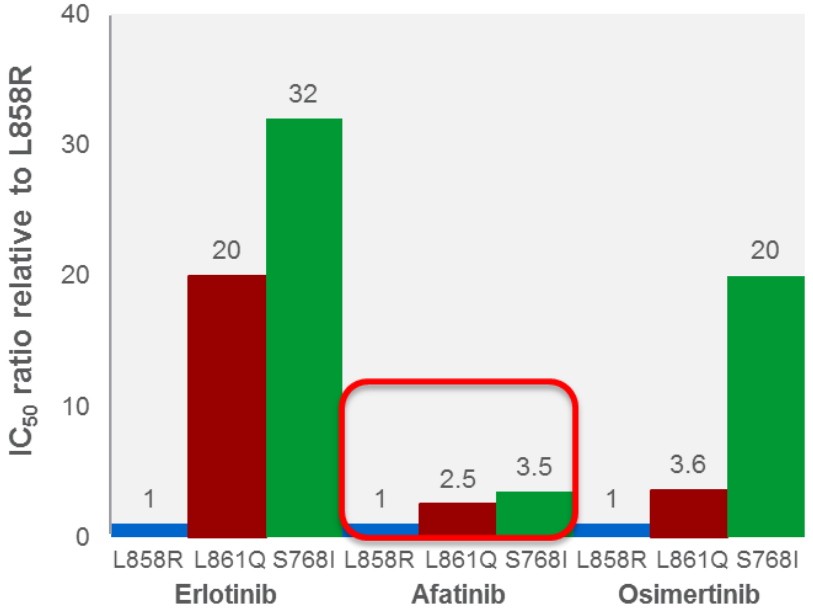
In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon *EGFR* Mutations (*cont'd*)

- 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

L858M/L861Q[1]



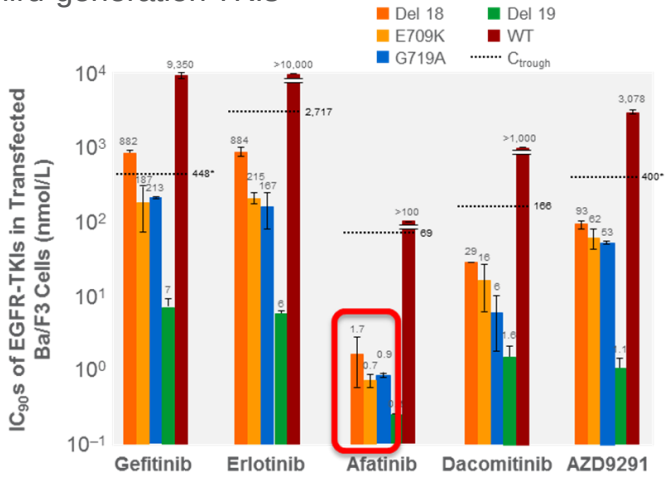
L861Q and S768I[2]

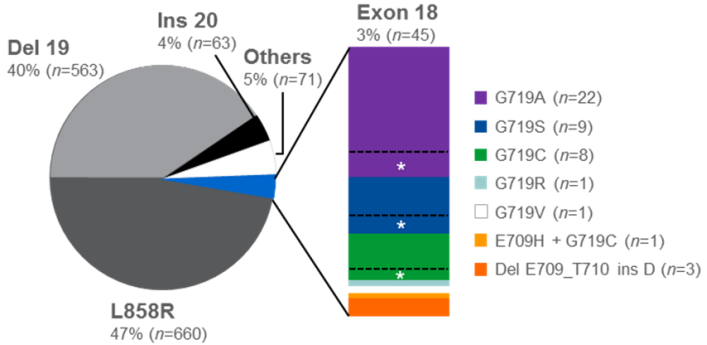


1. Saxon et al. *J Thorac Oncol*. 2017;12:884; 2. Banno et al. *Cancer Sci*. 2016;107:1134.

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

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

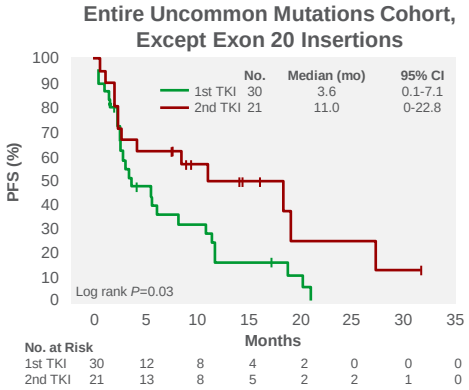


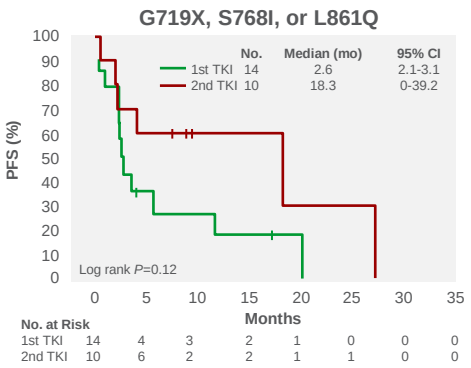


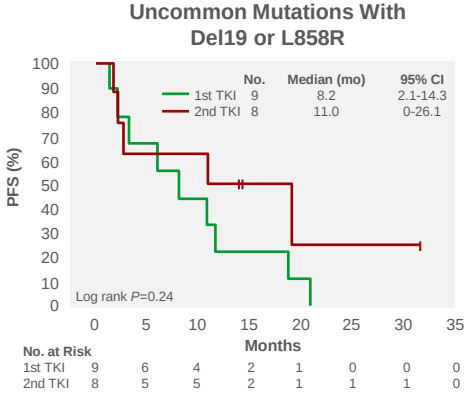
[a] Estimated trough concentration.
IC_{90} = 90% inhibitory concentration.
Kobayashi et al. *Clin Cancer Res*. 2015;21:5305.

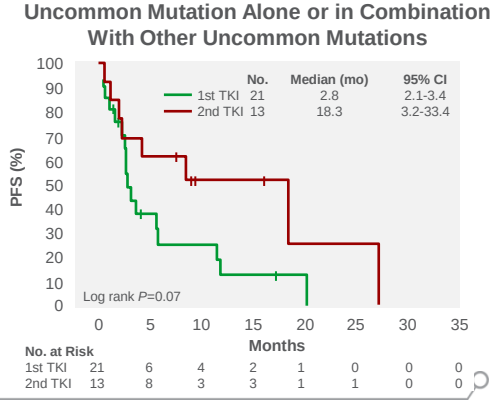
First-Line Clinical Data: Retrospective Analysis of PFS in 57 Patients Treated With Afatinib or First-Generation TKIs

- 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 vs 3.6 mo
  - G719X, S768I, or L861Q: 18.3 vs 2.6 mo
  - Uncommon mutations with Del19 or L858R: 11.0 vs 8.2 mo
  - Uncommon mutation alone or in combination with other uncommon mutations: 18.3 vs 2.8 mo





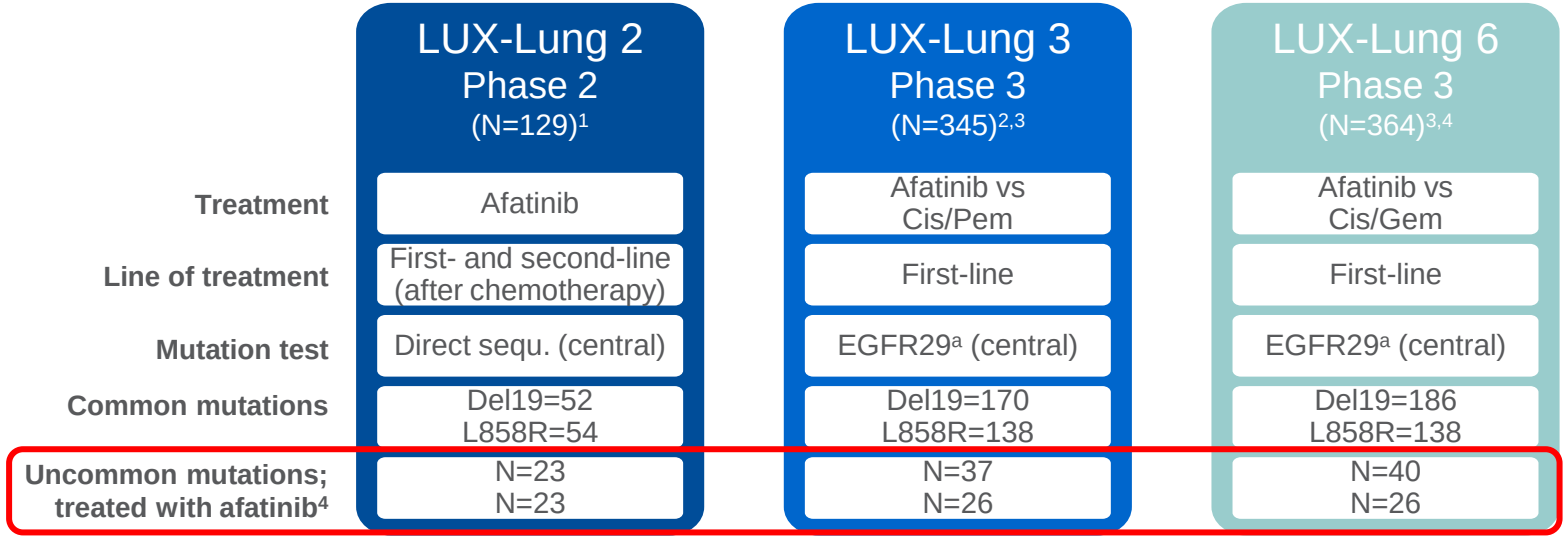




[a] Exon 20 insertions (except A763_Y764 insFQEA).
PFS = progression-free survival; CI = confidence interval.
Shen et al. *Lung Cancer*. 2017;110:56.

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

- Of 600 patients given afatinib in LUX-Lung 2/3/6, 75 patients (12.5%) had uncommon *EGFR* mutations[1]
- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations[1-4]

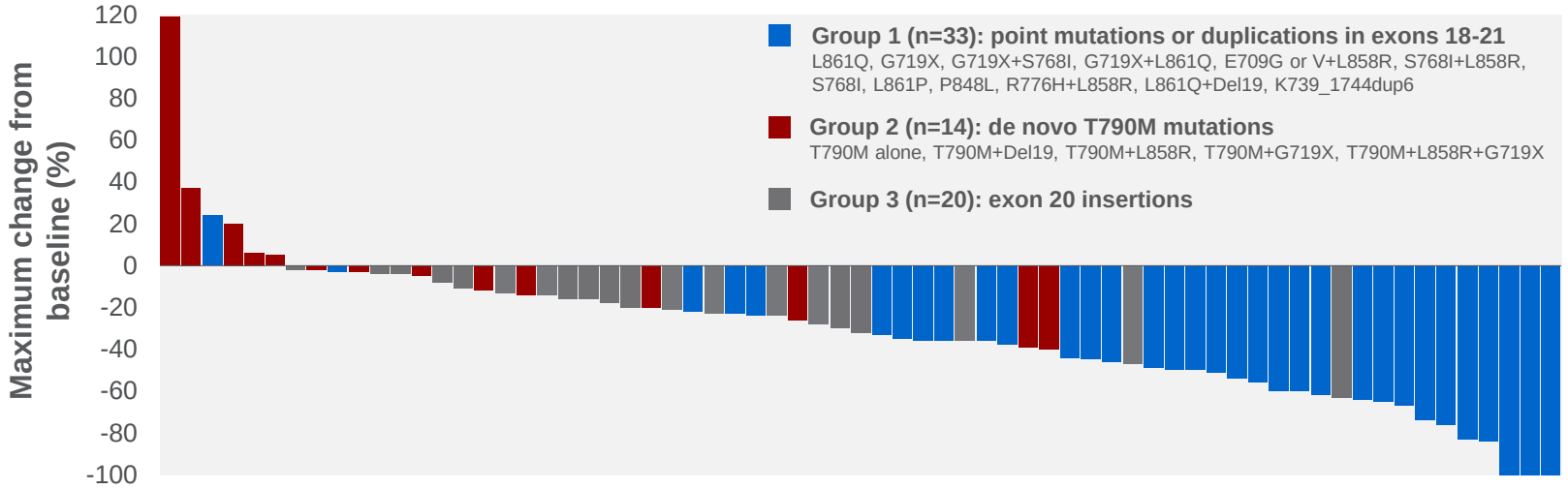


[a] EGFR mutations detected by the TheraScreen EGFR29 test. Common: 19 deletions in exon 19 and L858R in exon 21; Uncommon: 3 insertions in exon 20, L861Q, T790M, G719S, G719A and G719C, and S768I. Cis = cisplatin; Pem = pemetrexed; Gem = gemcitabine.

1. Yang et al. *Lancet Oncol*. 2012;13:539; 2. Sequist et al. *J Clin Oncol*. 2013;31:3327; 3. Yang et al. *Lancet Oncol*. 2015;16:830; 4. Wu et al. *Lancet Oncol*. 2014;15:213.

LUX-Lung 2, 3, and 6: Tumour Shrinkage by Independent Review (n=67[a])

- 3 patients in group 1 achieved complete response
  - 1 each with G719X, K739_1744dup6, and L858R+Q709G/V



[a] 8 patients were not included because of insufficient data.
Yang et al. *Lancet Oncol*. 2015;16:830.

LUX-Lung 2, 3, and 6: Response Rate, PFS, and OS by Independent Review

	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 (mo)	2.9	2.7	10.7	13.8	8.2	14.7
OS (mo)	14.9	9.2	19.4	26.9	17.1	NE

OS = overall survival; Mut/Dup = mutation/duplication; NE = not evaluable.
Yang et al. *Lancet Oncol*. 2015;16:830.

Responses[a] in Patients With NSCLC Harbouring Nonresistant *EGFR* Mutations From LUX-Lung 2, 3, and 6

- Among the 75 afatinib-treated patients with uncommon *EGFR* mutations, 32 patients had a nonresistant *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 (mo) (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

+response ongoing at time of censoring.
[a] IRC-assessed.
NA = not applicable; IRC = independent review committee.
GILOTRIF [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.

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. P1.01-98; 2. Brückl W. ESMO 2018. 1449P; 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)

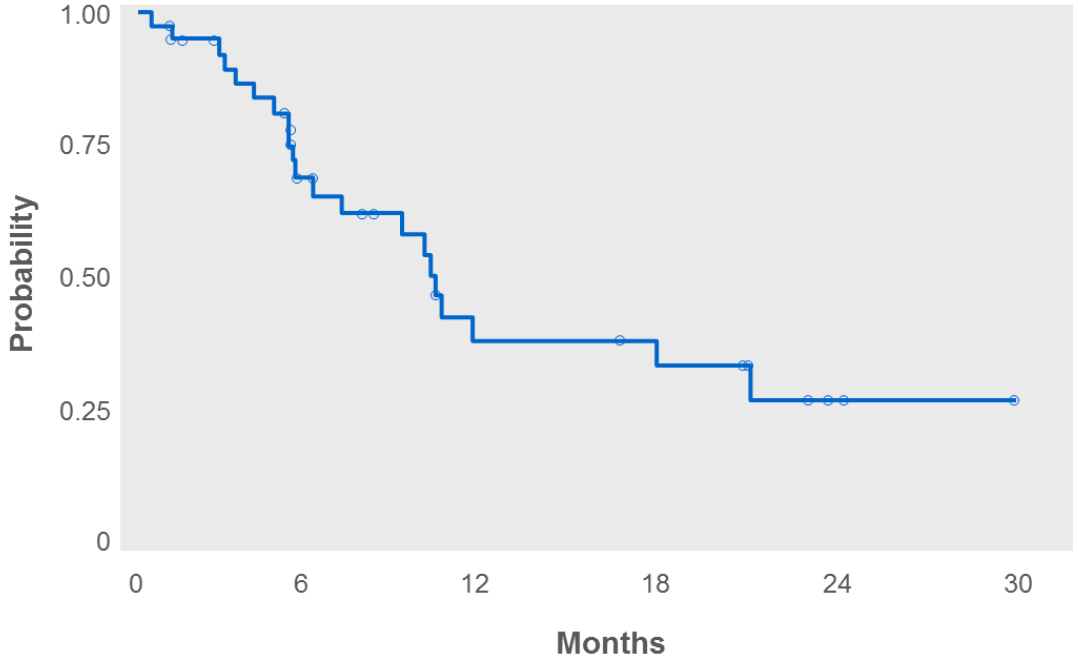
G719X	N (%)
CR	1 (5.3)
PR	10 (52.6)
SD	6 (31.6)
PD	2 (10.5)
ORR	**11 (57.9)**
DCR	17 (89.5)

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 with G719S/G719A/G719C; 3 patients with S768I/G719S/G719A/G719C; 2 patients with L861Q/G719S/G719A/G719C; 1 ptatien with 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.

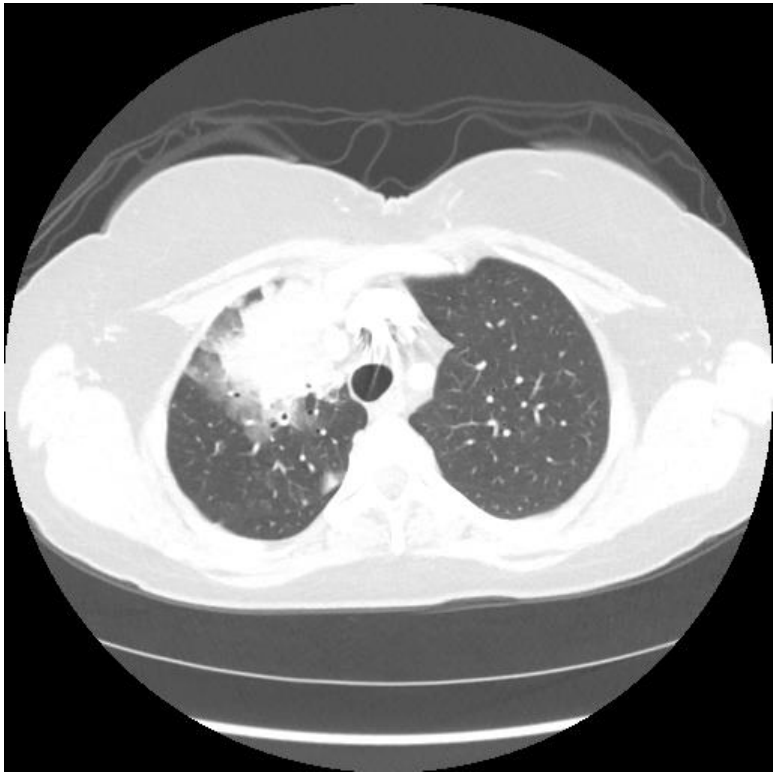
Patient Case: PM

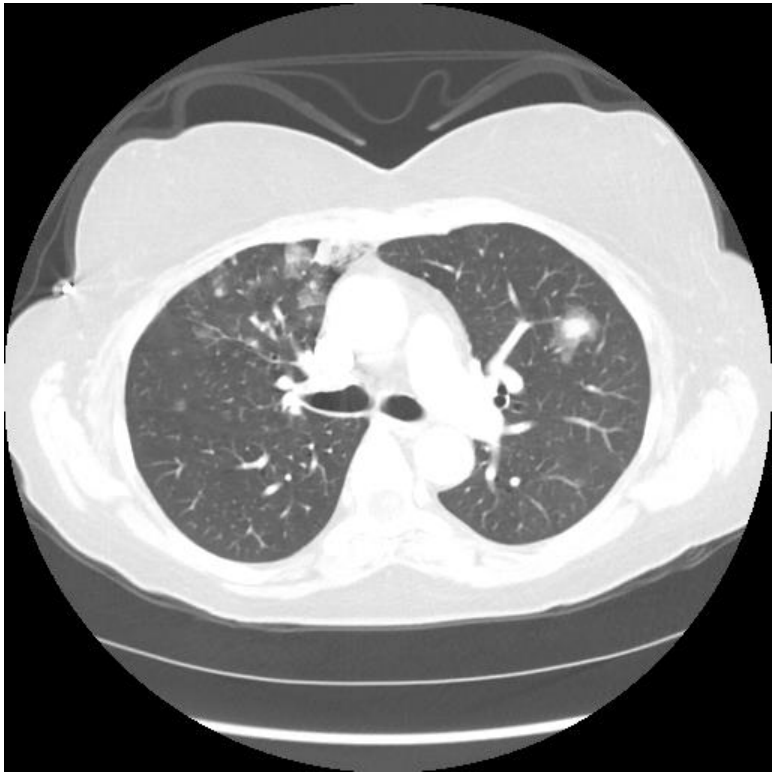
- PM is a 63-year-old white female who was in her usual state of health until November 2017, when she presented with complaints of cough and shortness of breath
- A chest x-ray revealed evidence of what was thought to be pneumonia. She was treated with antibiotics, but her symptoms did not improve
- She underwent a CT scan of the chest, which demonstrated a prominent RUL nodularity as well as ground glass opacities throughout both lungs
- She has no significant past medical history
- She has no tobacco or alcohol history

CT = computed tomography; RUL = right upper lobe.

Patient Case: PM (*cont'd*)

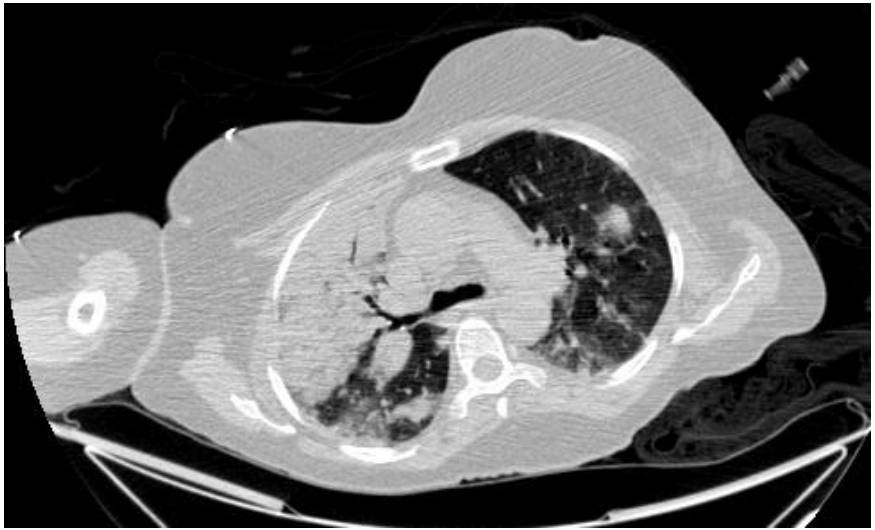
15 November 2017 – Baseline CT Scans





Patient Case: PM *(cont'd)*

- A biopsy of the lesion in the RUL demonstrated atypical cells, suspicious for adenocarcinoma. An additional CT-guided biopsy of the left lung yielded atypical glandular cells with marked acute inflammation
- PET/CT on 19 December 2017 identified an RUL malignancy and FDG avidity as well as "additional foci" within bilateral lungs
- MRI of the brain for staging purposes was performed on 4 January 2018 and was negative



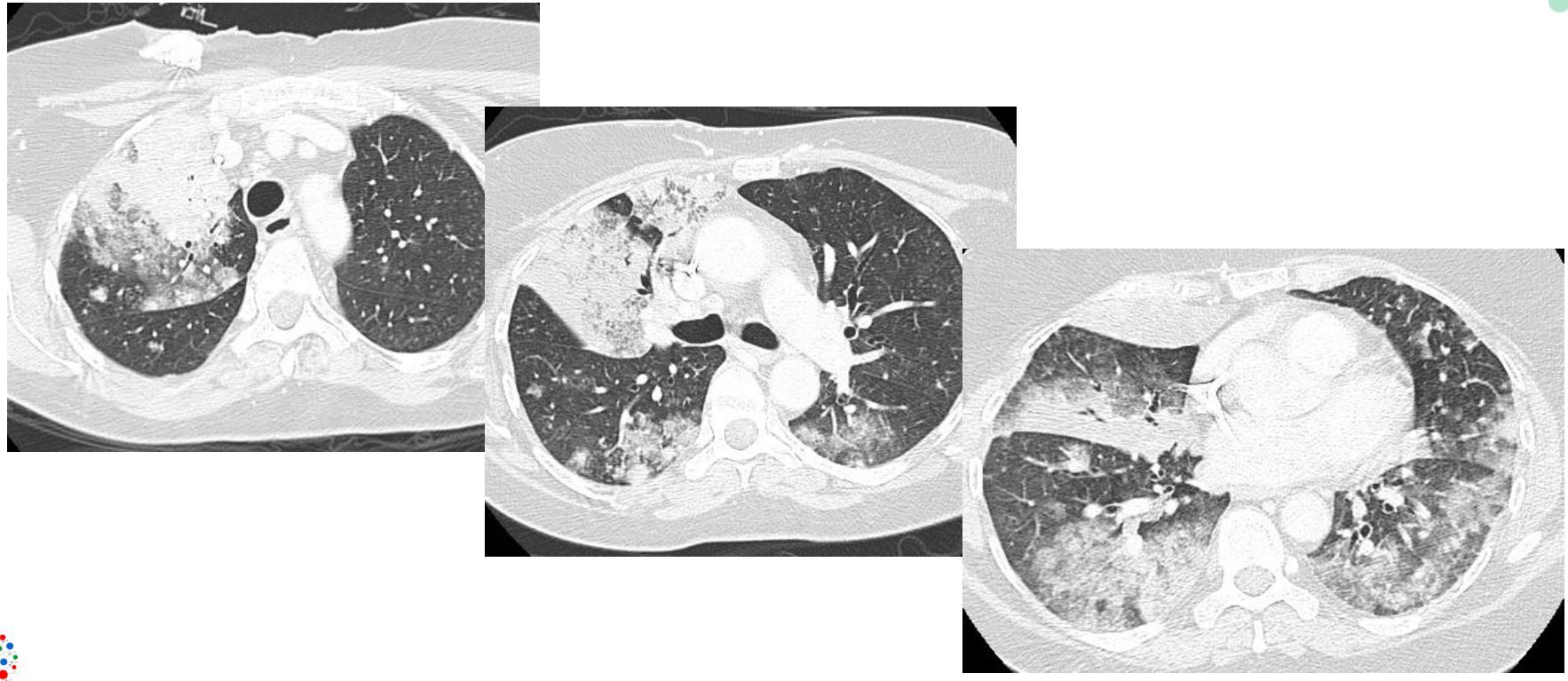
PET = positron emission tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging.

Patient Case: PM *(cont'd)*

- Based on the imaging presentation of cancer within bilateral lungs, it was thought to be stage IV disease with lymphangitic spread. With patient performance status declining, the patient was initiated on carboplatin/pemetrexed/pembrolizumab
- Following cycle 1, the carboplatin was dropped because of a possible patient allergy, which caused a rash, which she reported as occurring about 1 week after chemotherapy
- A repeat CT of the chest (abdominal) with contrast was performed on 20 February 2018 following 2 cycles of chemotherapy
- Blood biomarkers were analysed and revealed no presence of *EGFR*, *ALK*, or ROS1 mutations

Patient Case: PM *(cont'd)*

20 February 2018 — After 2 Cycles of Pemetrexed, Carboplatin, and Pembrolizumab



Patient Case: PM *(cont'd)*

- PM met with her oncologist and because of disease progression, based on imaging, and a reported PS of 3, hospice vs possible gemcitabine would be the most appropriate next course
- She was also initiated on high-dose steroids as well as antibiotics for possible pneumonitis as opposed to lymphangitic spread

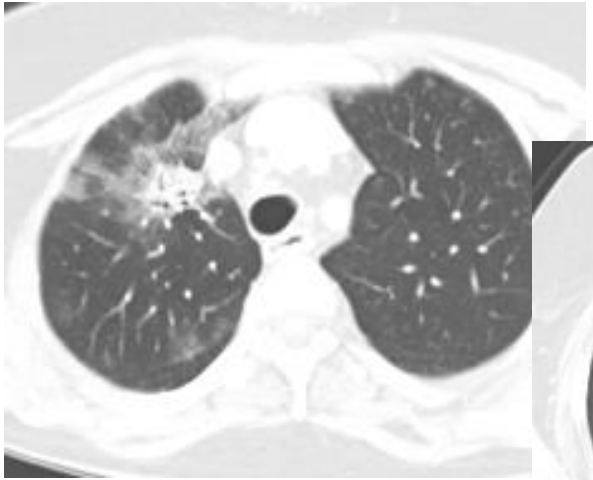
PS = performance status.

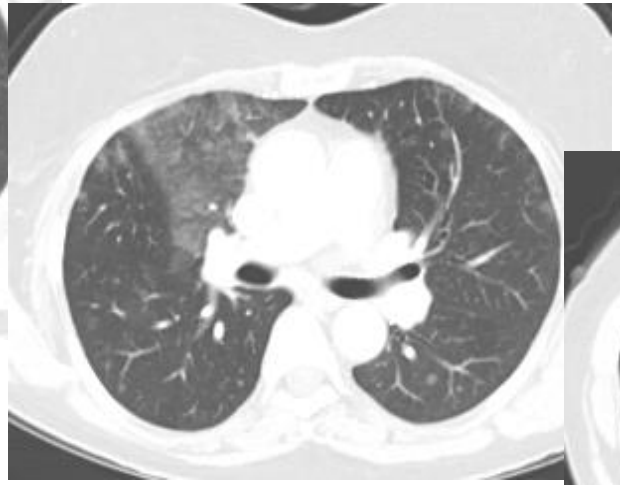
Patient Case: PM *(cont'd)*

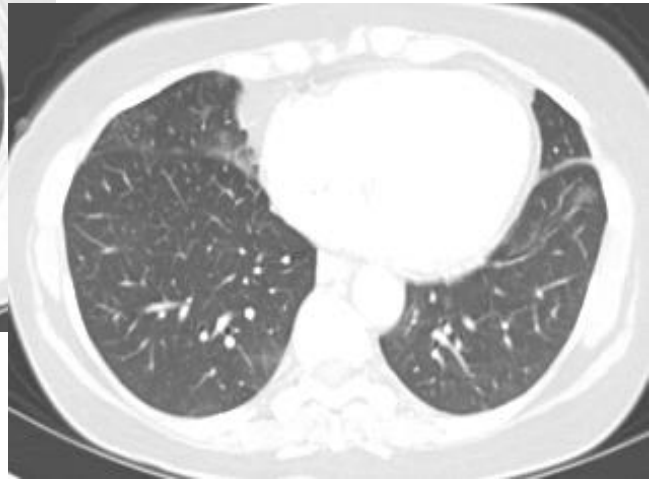
- Repeat blood markers were analysed (different platform) and revealed
  - Exon 21 uncommon mutation
- 14 March 2018: Patient started afatinib 30 mg daily
- 9 April 2018: Afatinib dosing held because of worsening diarrhoea
- 16 April 2018: Patient restarted on afatinib 20 mg, tolerated well

Patient Case: PM *(cont'd)*

27 June 2018 — After Afatinib Treatment







Patient Case: PM *(cont'd)*

Current State

- PM not using any oxygen (came off after the first month of afatinib treatment)
- Tolerating therapy well
- Just took a cruise

Summary

- Anecdotal data from erlotinib/gefitinib trials show variable and mainly limited responses to these EGFR TKIs in patients with NSCLC harbouring uncommon mutations
- Afatinib has shown preclinical and clinical 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 (Tamiya et al. *Anticancer Res.* 2017; 31:4177)
- 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 from real-world studies with afatinib are in line with analyses from the LUX-Lung trials
- These data could help inform clinical decisions for patients with NSCLC harbouring uncommon *EGFR* mutations

LMD = leptomeningeal disease.