Common Options for Uncommon Mutations

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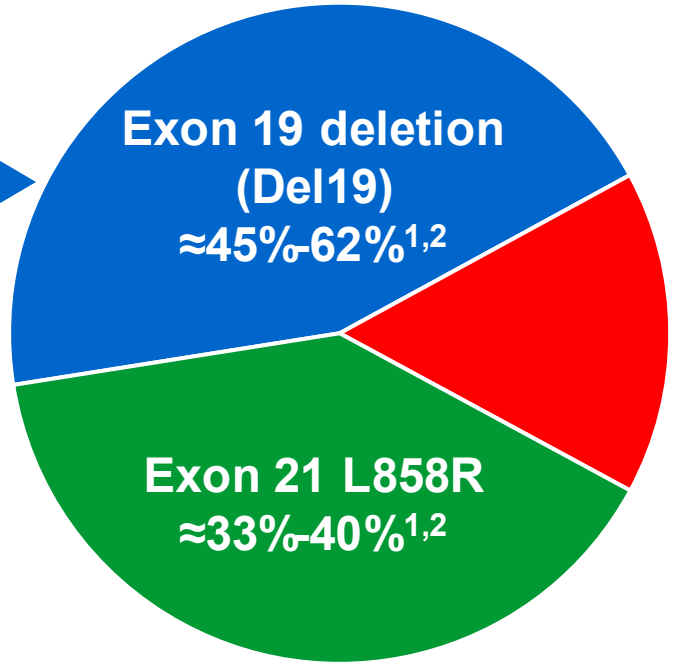
Disclosures

Has received honoraria for speeches or participated in compensated advisory boards for:

Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceutical, Daiichi Sankyo, AstraZeneca, Takeda, Hansoh Pharmaceutical, Blueprint Medicines, G1 Therapeutics

EGFR Mutations in NSCLC

The most frequent *EGFR* mutations in these populations are the common Del19 and/or L858R mutations[1,2]

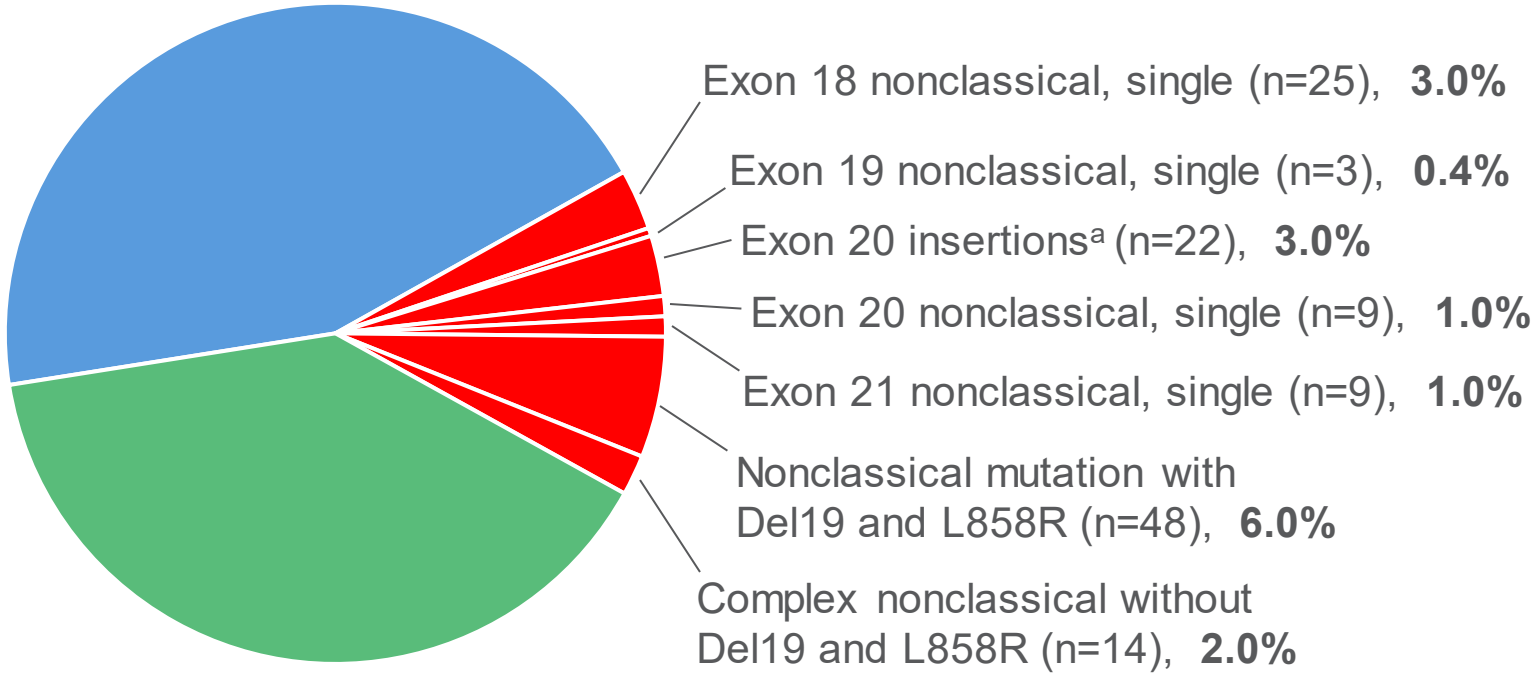


≈10%-15% of tumours harbour uncommon *EGFR* mutations, comprising mutations in exons 18-21[2,3]

1. Reguart and Remon. *Future Oncol.* 2015;11:1245; 2. Arrieta et al. Presented at 2018. Abstract 93; 3. Shen et al. *Lung Cancer.* 2017;110:56.

EGFR Mutations in NSCLC (*cont'd*)

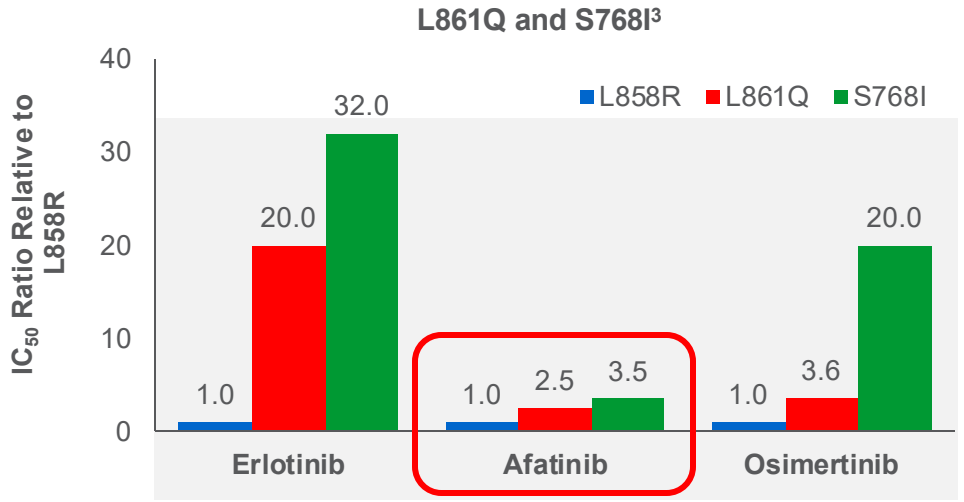
- Uncommon mutations consist of:
  - Exon 20 insertions (9%)
  - Uncommon mutations with Del19 or L858R complex mutations (30%)
  - Uncommon mutations alone or in combination with other uncommon mutations (61%)



[a]Exon 20 insertions (except A763_Y764 insFQEA).
EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer.
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 (L858R/L747S, L858R/D761Y, or L858R/T854A) in cell-based assays[1]
- First- and third-generation TKIs demonstrated reduced activity in cell lines harbouring uncommon mutations (L858M/L681Q,[2] L861Q,[3] and S768I[3]), whereas the afatinib response was similar across cell lines[2,3]



- Afatinib had greater sensitivity to exon 18 mutations (G719A, E709K, and Del18) than first- and third-generation TKIs[4]

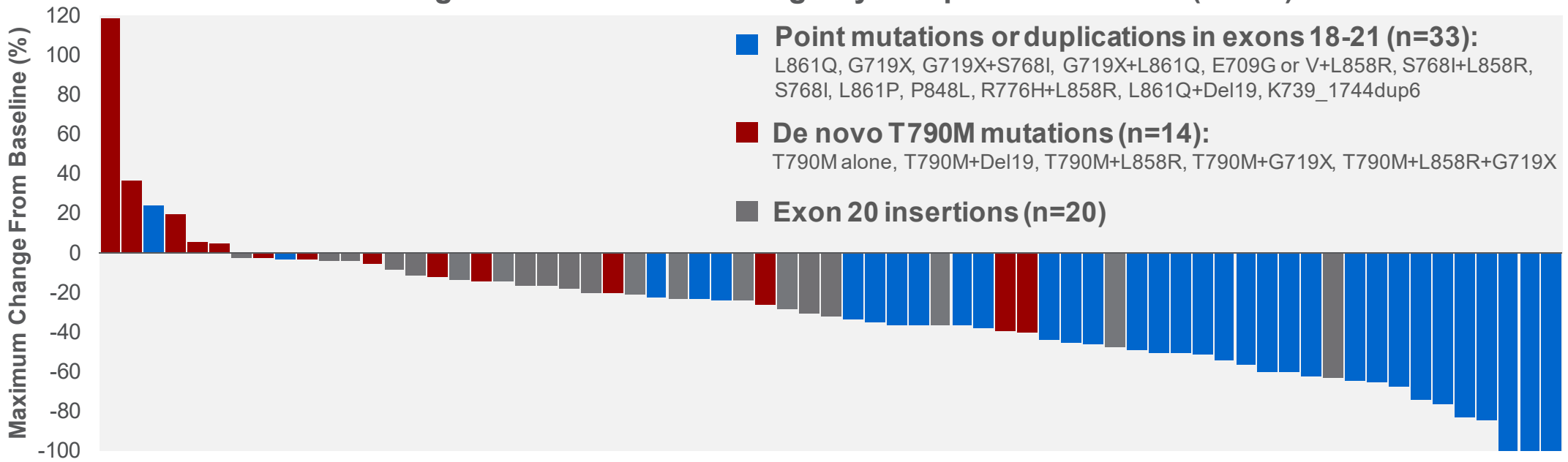
IC50 = half-maximal inhibitory concentration.

1. Chiba et al. *BMC Cancer*. 2017;17:281; 2. Saxon et al. *J Thorac Oncol*. 2017;12:884; 3. Banno et al. *Cancer Sci*. 2016;107:1134; 4. Kobayashi et al. Clin Cancer Res. 2015;21:5305.

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]
- 75 of 600 patients (12.5%) given afatinib harboured uncommon *EGFR* mutations in a combined post-hoc analysis of LUX-Lung 2/3/6[4]
  - 3 patients achieved CR; 1 each with G719X, K739_1744dup6, and L858R+E709G/V)

LUX-Lung 2/3/6: Tumour Shrinkage by Independent Review (n=67[a])[4]

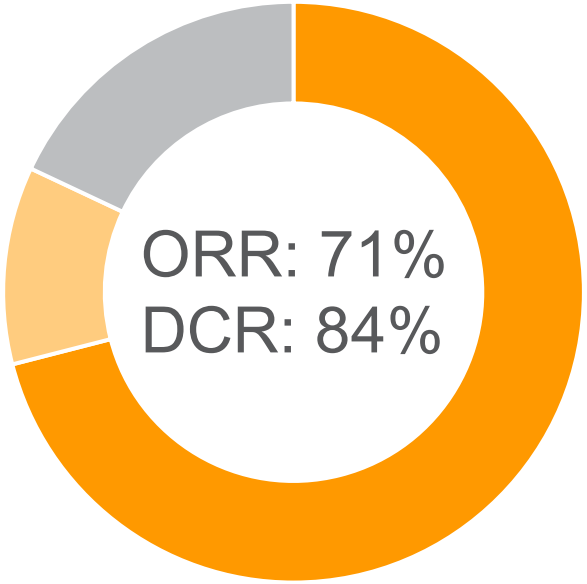


[a]8 patients were not included because of insufficient data.
CR = complete response.

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

Clinical Data: Response to Afatinib in NSCLC Harbouring Uncommon *EGFR* Mutations in LUX-Lung 2/3/6[1,2]

Point Mutations or Duplications in Exons 18-21, alone or in combination with each other[a] (n=38)



ORR by Mutation Type

S768I (n=8): 100%

G719X (n=18): 78%

L861Q (n=16): 56%

Median PFS (95% CI), months	10.7 (5.6-14.7)
Median OS (95% CI), months	19.4 (16.4-26.9)

- **De novo T790M mutations in exon 20, alone or in combination with other mutations** (n=14):
  - ORR: 14%; mPFS: 2.9 (95% CI: 1.2-8.3) months; mOS: 14.9 (95% CI: 8.1-24.9); DCR: 64.3% (n=9)
- **Exon 20 insertions** (n=23):
  - ORR: 9%; mPFS: 2.7 (95% CI: 1.8-4.2) months; mOS: 9.2 (95% CI: 4.1-14.2); DCR: 65.2% (n=15)

[a]Consists of patients with all point mutations or duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and rare others).

CI = confidence interval; DCR = disease control rate; mOS = median overall survival; mPFS = median progression-free survival; ORR = objective response rate; OS overall survival; PFS = progression-free survival.

1. Yang et al. *Lancet Oncol*. 2015;16:830; 2. Arrieta et al. Presented at LALCA 2018. Abstract 93.

First-Line Real-World Data: Retrospective Analysis of PFS in 56 Patients Treated With Afatinib or First-Generation TKIs[a]

- In all mutation groups analysed, the afatinib group exhibited longer mPFS compared with first-generation TKIs
  - Entire uncommon mutations cohort, except exon 20 insertions[b]: **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**

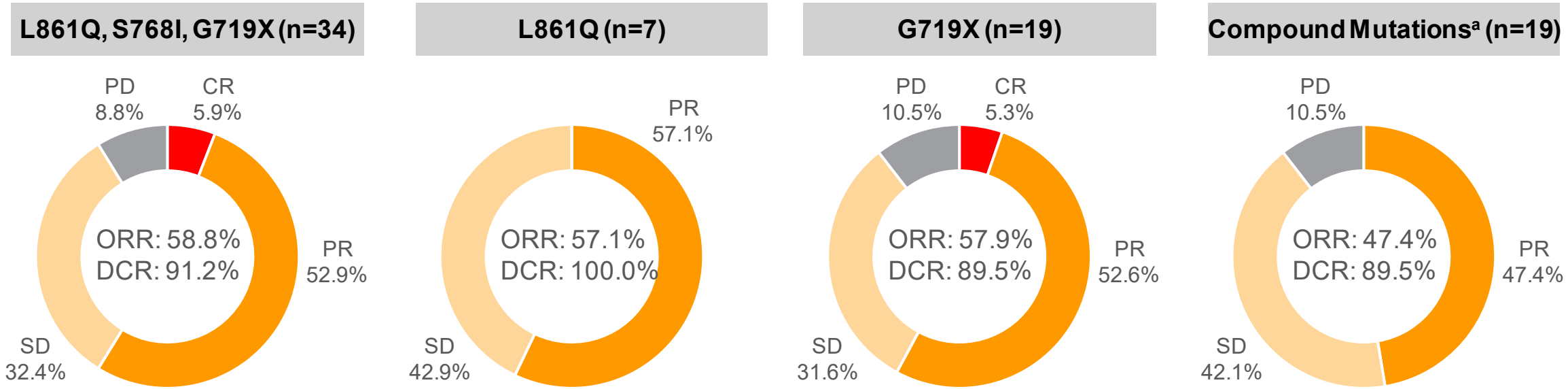
[a]Retrospective single-center, Chinese study of patients with stage IIIB-IV lung adenocarcinoma who underwent *EGFR* mutation testing from June 2011 to July 2016. 56 patients with non-classical mutations who received EGFR-TKI treatment and completed follow-up were included in the analysis.
[b]Exon 20 insertions (except A763_Y764 insFQEA).
Shen et al. *Lung Cancer.* 2017;110:56.

Prospective Real-World Data: Afatinib in EGFR TKI–naive Patients With Uncommon Mutations

Pooled Analysis From an Asian Phase 3b Study and a German Noninterventional Study

- In the combined analysis of subgroups with uncommon mutations (N=54), 5.6% of patients had an ECOG PS 2 at baseline

Best response to afatinib in *EGFR* mutation subgroups (by investigator review)



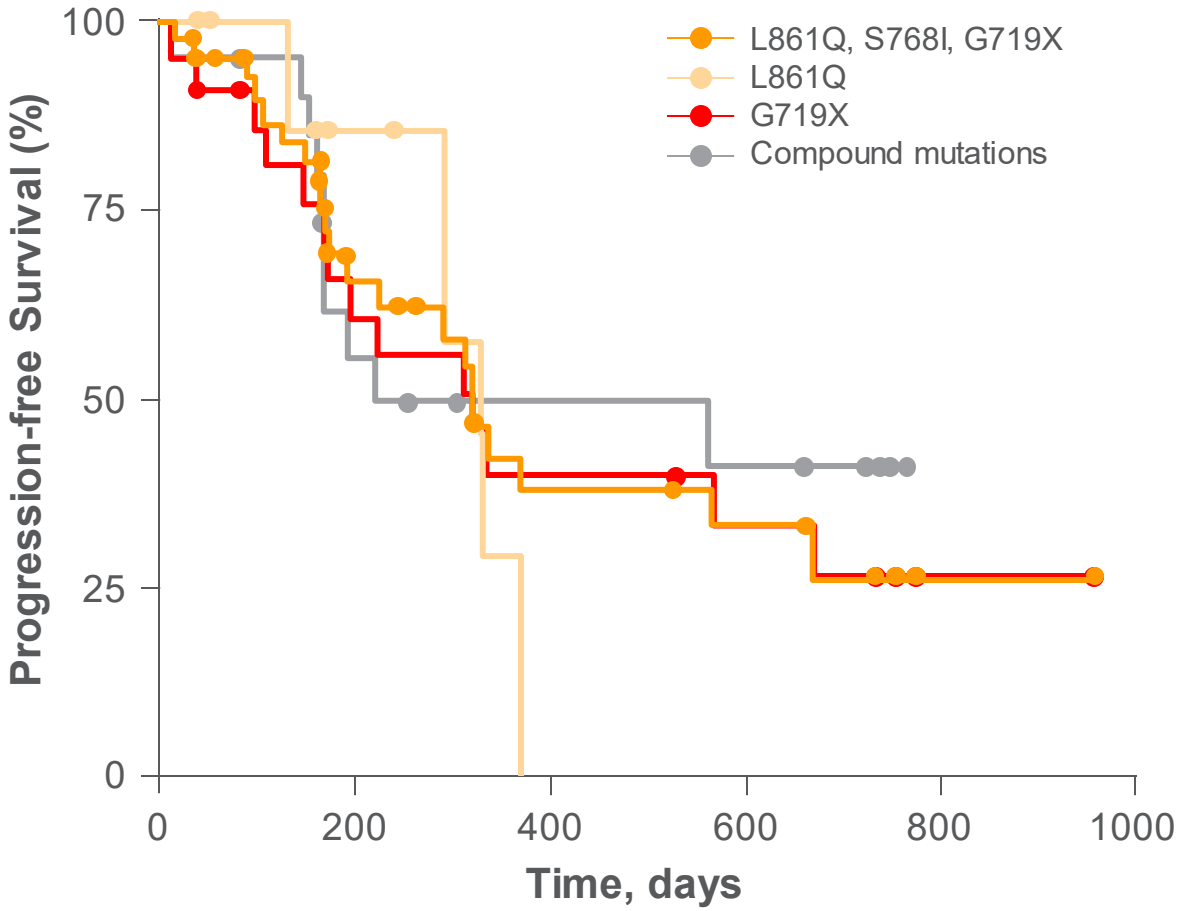
[a]11 patients with G719S/G719A/G719C; 3 patients with S768I/G719S/G719A/G719C; 2 patients with L861Q/G719S/G719A/G719C; 1 patient with S768I/L861Q/G719S/G719A/G719C; 1 patient each with G719A/L747V; L858A/T854A; del exon 18/ins exon 20; delins exon 20/delins exon 20.

ECOG = Eastern Cooperative Oncology Group; NIS = noninterventional study; CR = complete response; PD = progressive disease; PR = partial response; PS = performance status; SD = stable disease.

Maerten et al. *Asia Pac J Clin Oncol*. 2019;14(S7):abstract 337 (poster presentation).
ESMO 2019, Barcelona, Spain, 29 September 2019

Prospective Real-World Data With Afatinib in EGFR TKI–naive Patients With Uncommon Mutations *(cont'd)*: PFS

PFS in *EGFR* Mutation Subgroups



EGFR mutation	Median PFS (months)
L861Q, S768I, G719X (n=40)	10.7
L861Q (n=9)	10.7
G719X (n=14)	10.6
Compound mutations (n=20)	7.3

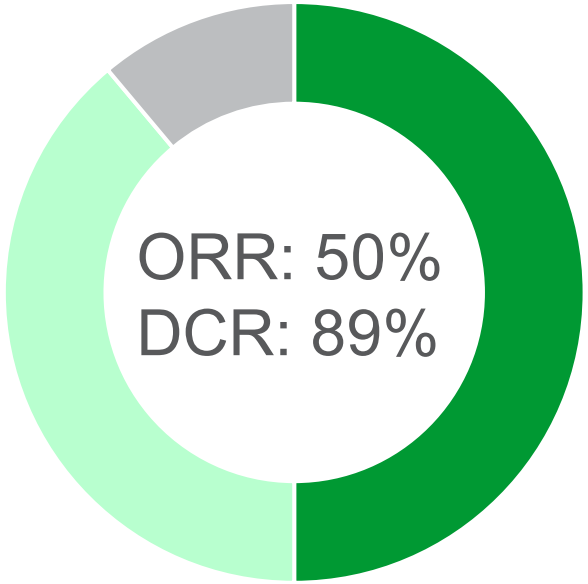
[a]11 patients with G719S/G719A/G719C; 3 patients with S768I/G719S/G719A/G719C; 2 patients with L861Q/G719S/G719A/G719C; 1 patient with S768I/L861Q/G719S/G719A/G719C; 1 patient each with G719A/L747V; L858A/T854A; del exon 18/ins exon 20; delins exon 20/delins exon 20.

Maerten et al. *Asia Pac J Clin Oncol*. 2019;14(S7):abstract 337 (poster presentation).

KCSG-LU15-09: Phase 2 Trial of Osimertinib in Patients With Uncommon *EGFR* m+ NSCLC

- All patients included in this analysis (N=36) had an ECOG PS 0-1 at baseline

Osimertinib in Uncommon *EGFR* m+ NSCLC



ORR by Mutation Type[a]

S768I (n=8): 37.5%

G719X (n=19): 52.6%

L861Q (n=9): 77.8%

Median PFS (range), months	9.5 (1.0-20.1)
Median DoR (95% CI), months	7.0 (4.7-9.3)

- The most common AEs (≥15%, all grade) were rash, anorexia, and diarrhea

Data cutoff November 2017.

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

AE = adverse event; DoR = duration of response; *EGFR* m+ = epidermal growth factor receptor mutation–positive.

Ahn et al. *J Clin Oncol*. 2018;36(15_suppl):9050 (poster presentation).

Ongoing Investigations of Antitumor Activity in Patients With EGFR Exon 20 Mutant NSCLC

- Poziotinib in Exon 20 mutant EGFR m+ NSCLC (n=44) - Phase 2[1]
  - ORR (best response): 55%
  - ORR (confirmed): 43%

- TAK-788 in Exon 20 insertion EGFR m+ NSCLC (n=28) - Phase 1/2[2]
  - ORR: 43%
  - DCR: 86%

- JNJ-372, an EGFR-cMet bispecific ab, in Exon 20 insertion EGFR m+ NSCLC (n=27) - Phase 1[3]
  - 8/27 (30%) patients with best response of PR (6 confirmed)

Ab = antibody.

1. Heymach et al. *J Thorac Oncol*. 2018;13:S323; 2. Jänne et al. Presented at ASCO 2019. Abstract 9007; 3. Haura et al. *J Clin Oncol*. 2019:37(suppl; abstr 9009).

Summary

- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations[1-4]
- Afatinib had clinically meaningful activity in NSCLC tumours harbouring point mutations or duplications in exons 18-21 (eg, G719X, S768I, L861Q K739_1744dup6, and L858R+E709G/V)[4]
- Data from real-world studies with afatinib are in line with analyses from the LUX-Lung trials[5,6]
- Limited data (n=36) with osimertinib from a Korean phase 2 study show activity in the major uncommon mutations[7]
- Emerging studies highlight new compounds targeting EGFR exon 20 insertions (poziotinib, TAK-788, JNJ-372) [8-10]
- Taken together, we are making progress in the use of targeted therapy for the treatment of NSCLC with uncommon EGFR mutations

CUP = compassionate use programme; EAP = expanded-access programme.

1. Yang et al. *Lancet Oncol*. 2012;13:539; 2. Sequist et al. *J Clin Oncol*. 2013;31:3327; 3. Wu et al. *Lancet Oncol*. 2014;15:213; 4. Yang et al. *Lancet Oncol*. 2015;16:830; 5. Shen et al. *Lung Cancer*. 2017;110:56; 6. Maerten et al. *Asia Pac J Clin Oncol*. 2019;14(S7):abstract 337; 7. Ahn et al. *J Clin Oncol*. 2018;36(15_suppl):9050; 8. Heymach et al. *J Thorac Oncol*. 2018;1:3S323; 9. Jänne et al. *J Clin Oncol*. 2019;37(suppl):abstract 9007; 10. Haura et al. *J Clin Oncol*. 2019:37(suppl; abstr 9009).