# Sequencing of therapy following first-line afatinib in patients with *EGFR* mutation-positive (*EGFR*m+) non-small-cell lung cancer

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# Introduction

- Afatinib, an irreversible ErbB family blocker, is approved in many countries, including China,[1] for the first-line treatment of patients with advanced *EGFR*m+ NSCLC
- Due to acquired resistance to EGFR TKIs such as afatinib, subsequent therapies must be evaluated to determine optimal sequencing
- We analyzed outcomes with subsequent therapies following first-line afatinib in the LUX-Lung (LL) 3, 6 and 7 clinical studies

**LL3 and LL6 studies (Phase III)**

- Afatinib significantly improved PFS and OR versus platinum-doublet chemotherapy in patients with *EGFR*m+ NSCLC[2,3]
- Afatinib significantly prolonged OS versus chemotherapy in a prespecified subgroup analysis of patients with *EGFR* Del19 mutation[4] and in a post-hoc analysis of Chinese patients with *EGFR* Del19 mutation[5]

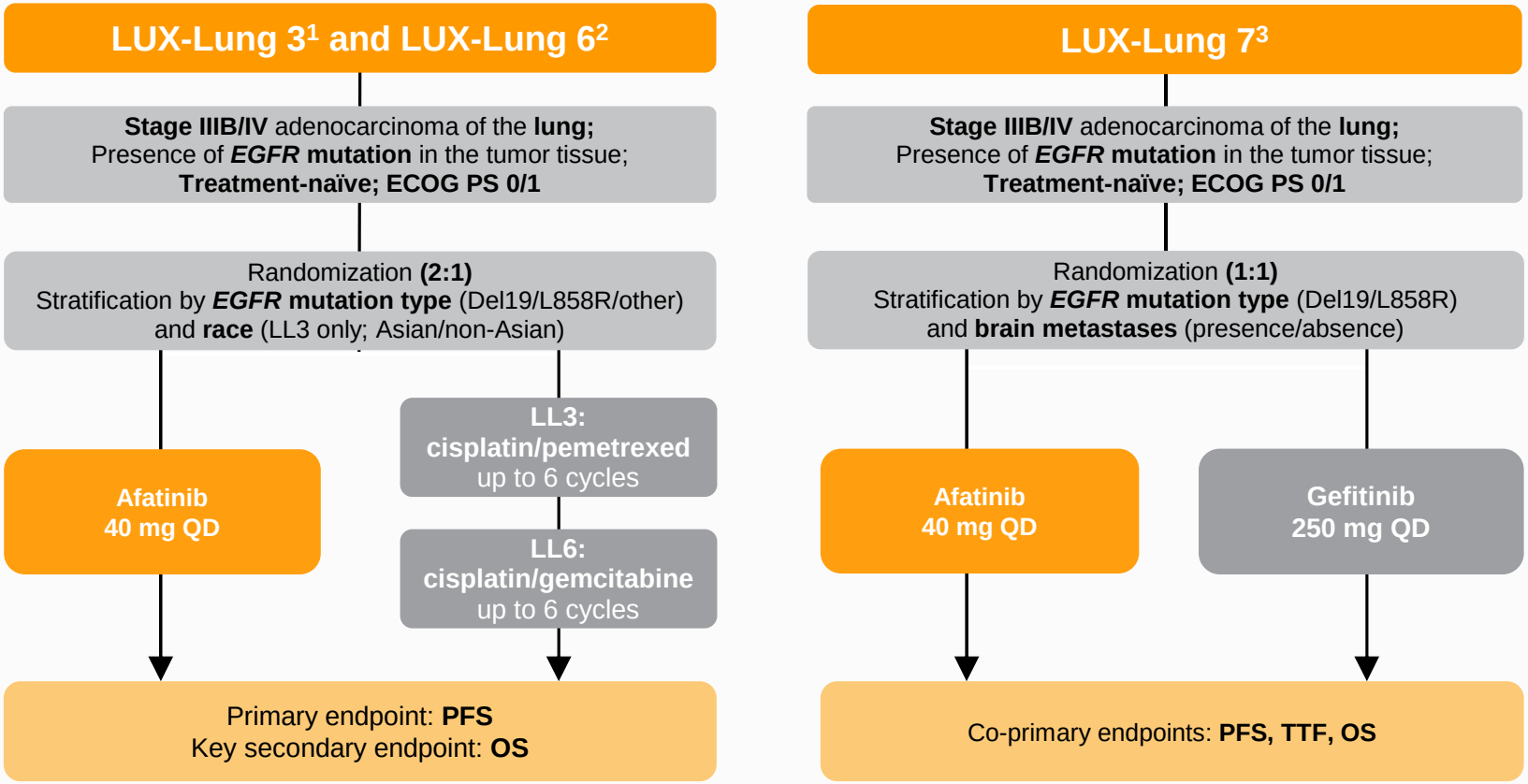
**LL7 study (Phase IIb)**

- Afatinib significantly improved PFS, TTF, and OR versus gefitinib in the same setting[6]
- There was no significant difference in OS, but a trend towards improved OS with afatinib versus gefitinib[7]

EGFRm+, EGFR mutation-positive; OR, objective response; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure.

1. https://www.boehringer-ingelheim.com/press-release/afatinib-approved-lung-cancer-china. Accessed August 2018;
2. Sequist LV, et al. J Clin Oncol 2013;31:3327–34; 3. Wu Y-L, et al. Lancet Oncol 2014;2:213–22;
4. Yang JC, et al. Lancet Oncol 2015;2:141–51; 5. Wu Y-L, et al. OncoTargets Ther. In Press;
6. Park K, et al. Lancet Oncol 2016;5:577–89; 7. Corral J. Ann Oncol 2017;28:ii28–51

# Study designs




QD, every day; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

1. Sequist LV, et al. J Clin Oncol 2013;31:3327–34;
2. Wu Y-L, et al. Lancet Oncol 2014;2:213–22;
3. Park K, et al. Lancet Oncol 2016;5:577–89

# Methodology

- Retrospective analysis of subsequent therapy outcomes in patients with common *EGFR* mutations (Del19, L858R) in LUX-Lung 3, 6 and 7
  - Subsequent therapy was decided by the treating physician
- Data were collected prospectively as study follow-up information
- Biopsies at afatinib discontinuation were not required
- Data cut-offs:
  - LUX-Lung 3 and 6: March 25, 2016
  - LUX-Lung 7: August 20, 2017

# Subsequent therapy in patients who discontinued afatinib

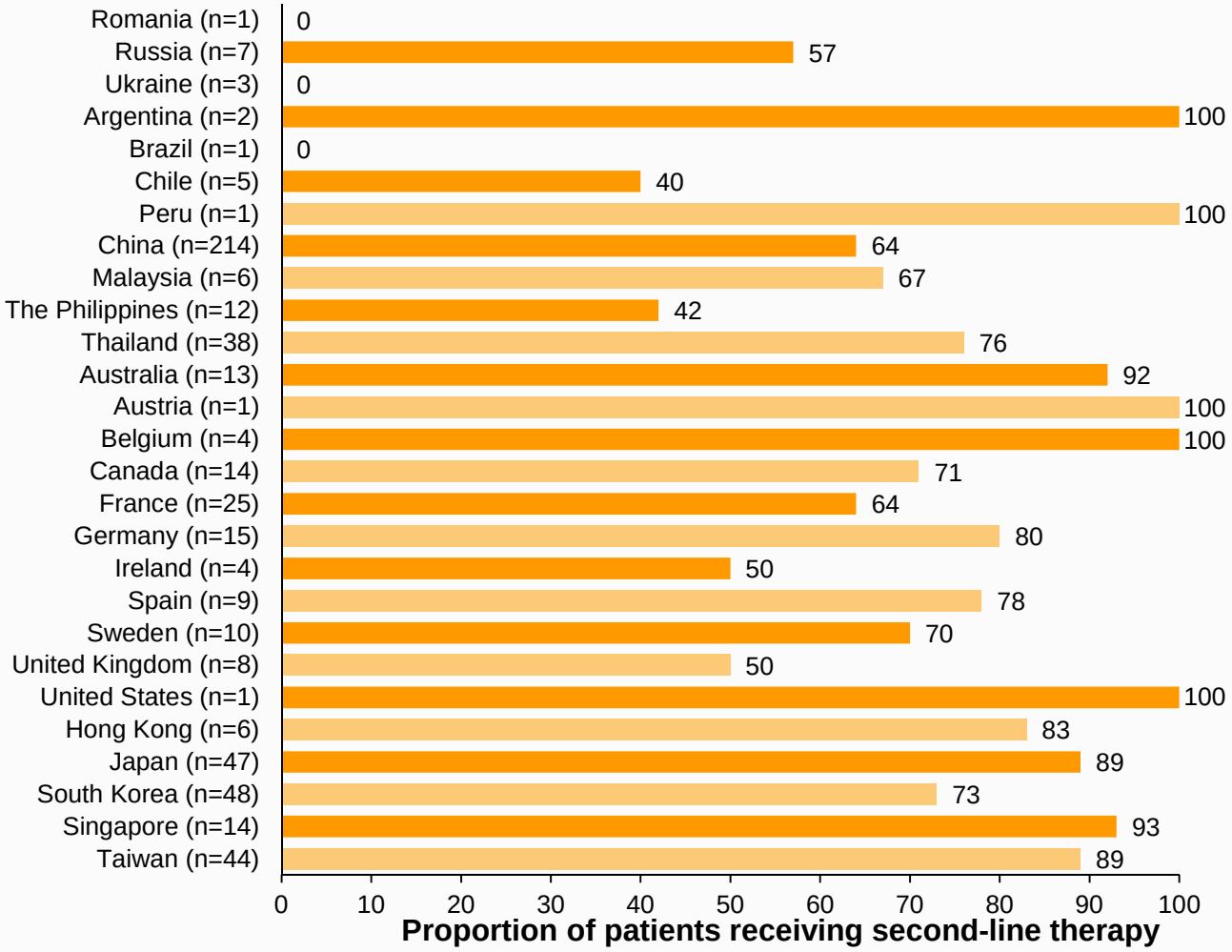
n = 579 — Common *EGFR* mutations; randomized to afatinib

n = 553 — Discontinued afatinib at time of analysis*

| | Any subsequent systemic treatment | Platinum-based CT | Single-agent CT | First-generation TKI monotherapy† | Other‡ |
|---|---|---|---|---|---|
| **Any-line treatment** | 394 (71%) | 277 (50%) | 181 (33%) | 186 (34%) | 121 (22%) |
| **Second-line treatment** | 394 (71%) | 252 (46%) | 39 (7%) | 49 (9%) | 54 (10%) |
| **Third-line treatment** | 265 (48%) | 48 (9%) | 104 (19%) | 75 (14%) | 38 (7%) |
| **Fourth-line treatment** | 156 (28%) | 27 (5%) | 50 (9%) | 49 (9%) | 30 (5%) |

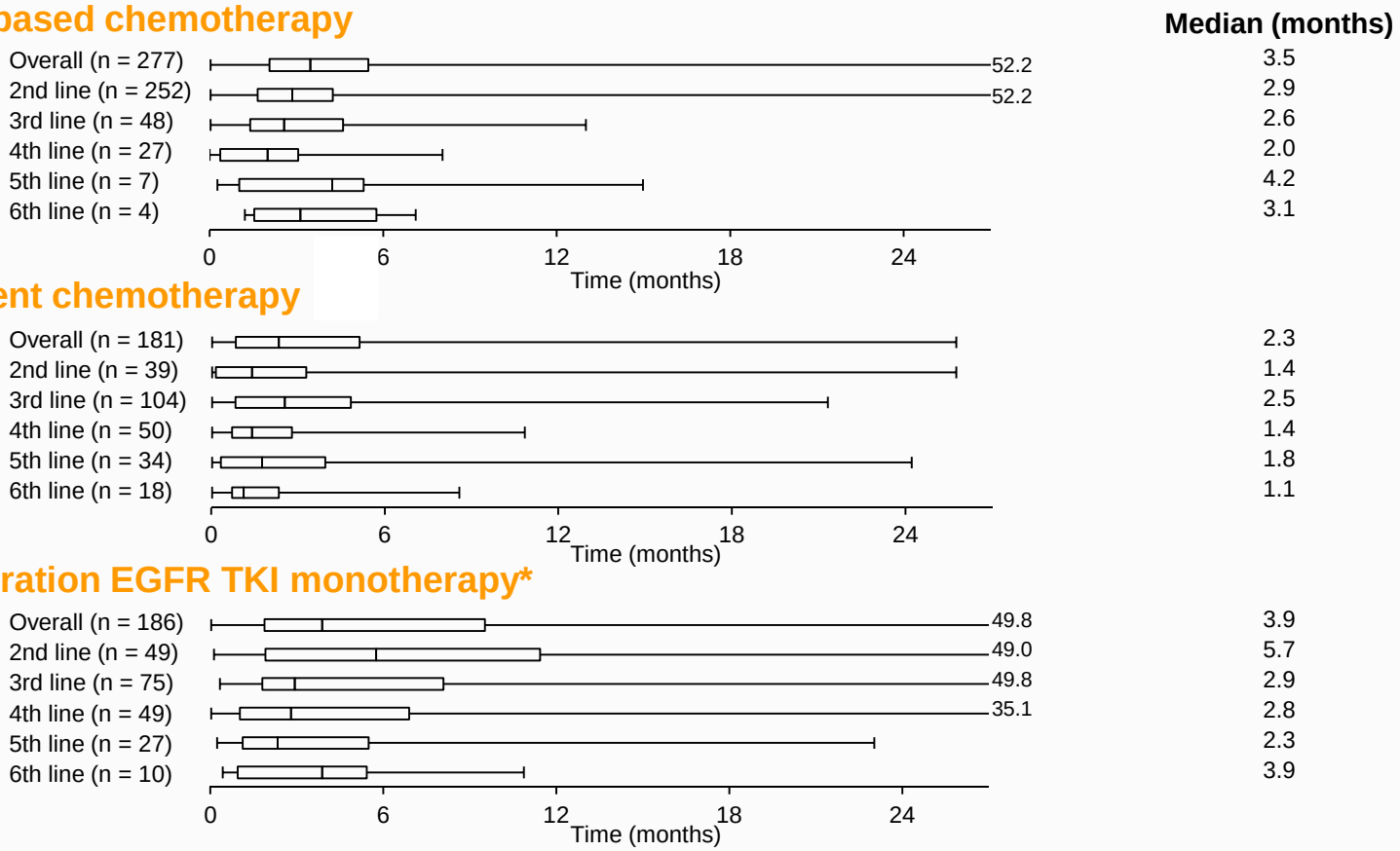
Percentages are of the total number of patients who discontinued afatinib (n=553). *Data cut-off for Lux-Lung 7: December 2016; †Erlotinib, gefitinib and icotinib; ‡Includes: platinum-based, single-agent and other CT combination therapies; osimertinib, afatinib, HM61713 and rociletinib monotherapies; erlotinib-, gefitinib-, icotinib- and afatinib-containing combinations; immune checkpoint inhibitors; and 'other' therapies. CT, chemotherapies.

# Uptake of second-line treatment by country




Countries are grouped according to similar reimbursement policies; Data cut-off for LUX-Lung 7: December 2016.

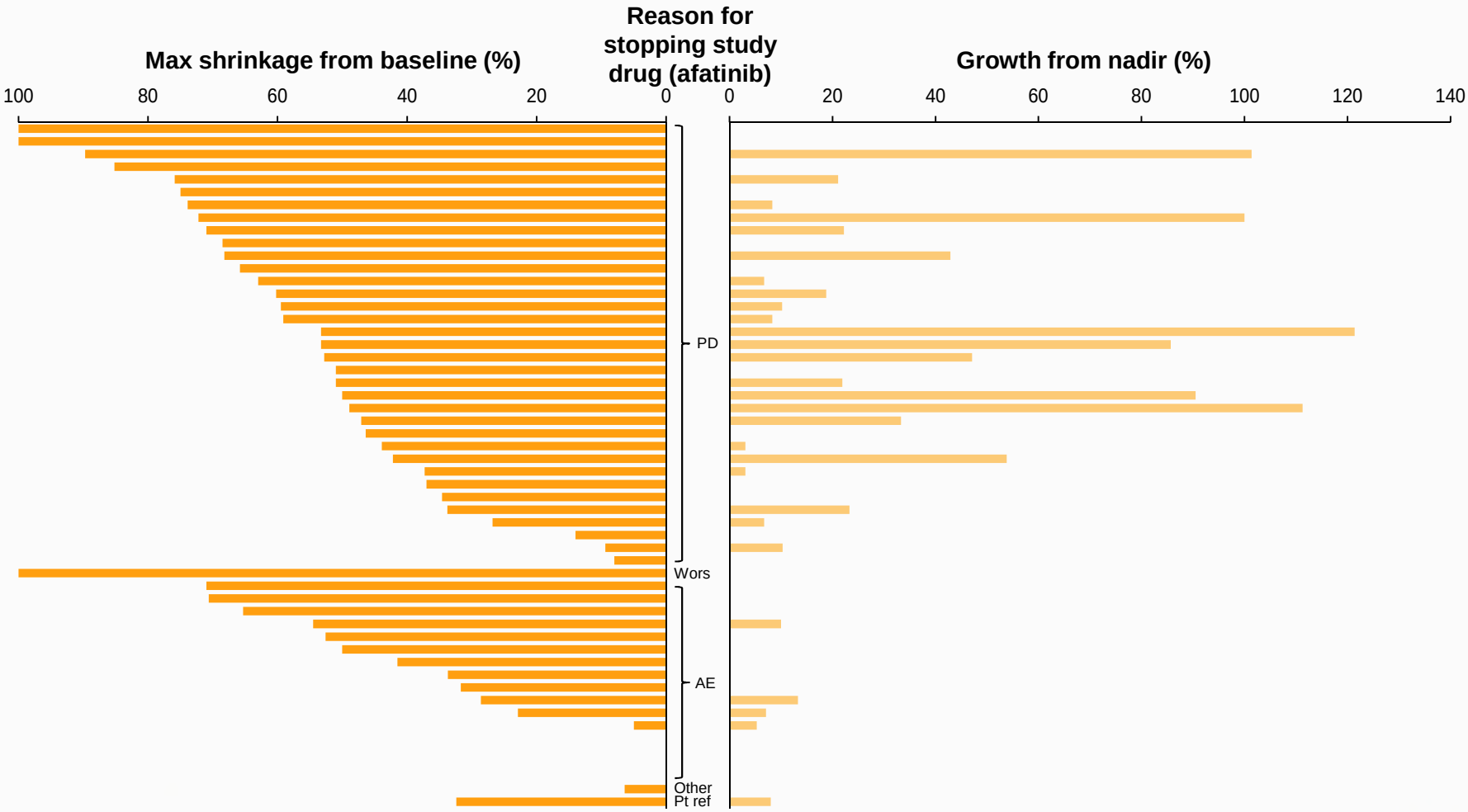
# Time on subsequent treatment following discontinuation of first-line afatinib




**Time on first-generation EGFR TKI monotherapy post-afatinib was longest in the second-line setting**

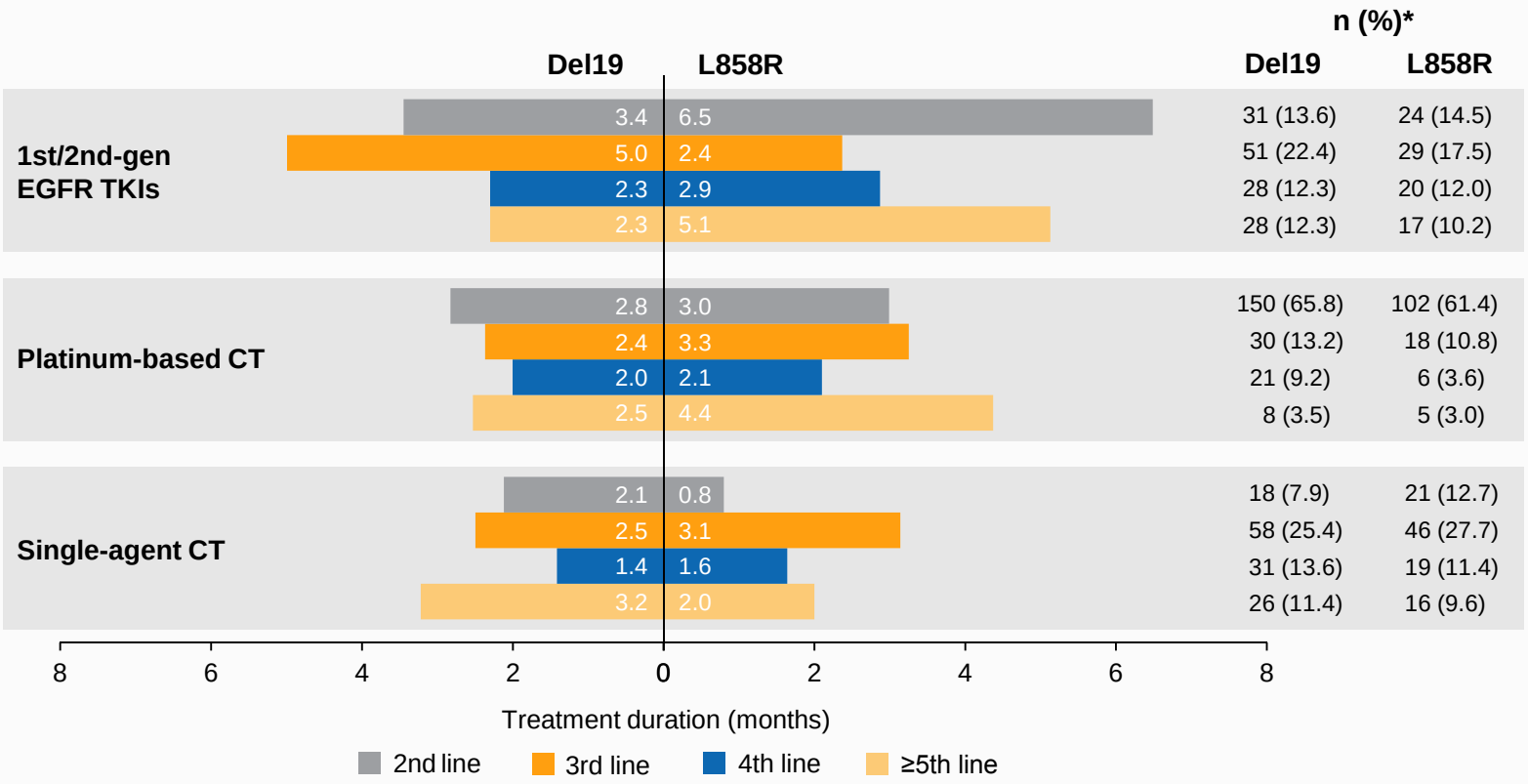
*Erlotinib, gefitinib and icotinib monotherapy; Data cut-off for LUX-Lung 7: December 2016.

# Tumor shrinkage and subsequent re-growth in patients treated with second-line EGFR TKIs




Data cut-off for LUX-Lung 7: December 2016.
AE, adverse event; Pt ref, patient refusal; Wors, worsening of underlying cancer disease.

# Impact of *EGFR* mutational subtype on subsequent therapy following first-line afatinib



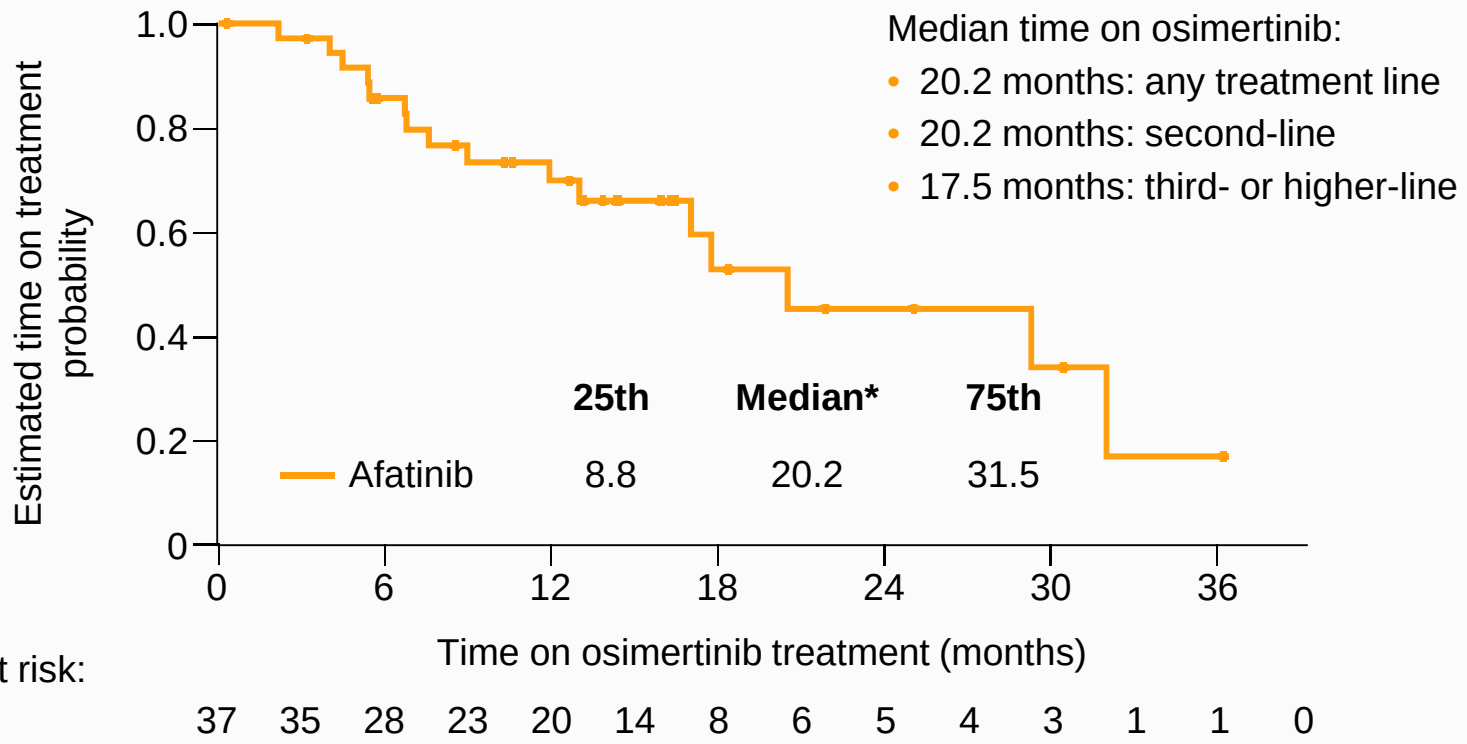

*Percentage of patients who received ≥1 subsequent therapy (Del19 n=228; L858R n=166); Data cut-off for LUX-Lung 7: December 2016.

# Baseline characteristics of patients who received osimertinib in any line following first-line afatinib or gefitinib

| Study | LL3, 6 & 7 | LUX-Lung 7 | | | |
|---|---|---|---|---|---|
| First-line study drug | Afatinib | Afatinib | | Gefitinib | |
| Subsequent therapy | Osimertinib (n = 37)* | Any or none (n = 160) | Osimertinib (n = 27) | Any or none (n = 159) | Osimertinib (n = 23) |
| Female, % | 67.6 | 56.9 | 66.7 | 66.7 | 87.0 |
| Median age, years (range) | 59 (35–78) | 63 (30–86) | 61 (37–78) | 63 (32–89) | 67 (44–81) |
| Asian, % | 54.1 | 58.8 | 44.4 | 55.3 | 43.5 |
| Never smoked, % | 78.4 | 66.3 | 74.1 | 66.7 | 82.6 |
| ECOG PS 0, % | 40.5 | 31.9 | 37.0 | 29.6 | 34.8 |
| *EGFR* Del19 mutation, % | 62.2 | 58.1† | 55.6 | 58.5 | 73.9 |
| Brain metastases at screening, % | 5.4 | 16.3 | 7.4 | 15.1 | 13.0 |
| Median exposure to study drug, months | 21.9 | 13.7 | 17.5 | 11.5 | 17.9 |
| Osimertinib<br>Second-line, %<br>≥Third-line, % | <br>27.0<br>73.0 | <br>–<br>– | <br>33.3<br>66.7 | <br>–<br>– | <br>21.7<br>78.3 |

*Patients with common *EGFR* mutations only; †One patient in the afatinib group with wild-type *EGFR* was erroneously included in the trial and was reported as *EGFR* Del19 mutation at the time of randomization.
LL, LUX-Lung.

# Time on osimertinib in patients who received subsequent osimertinib in any treatment line following first-line afatinib

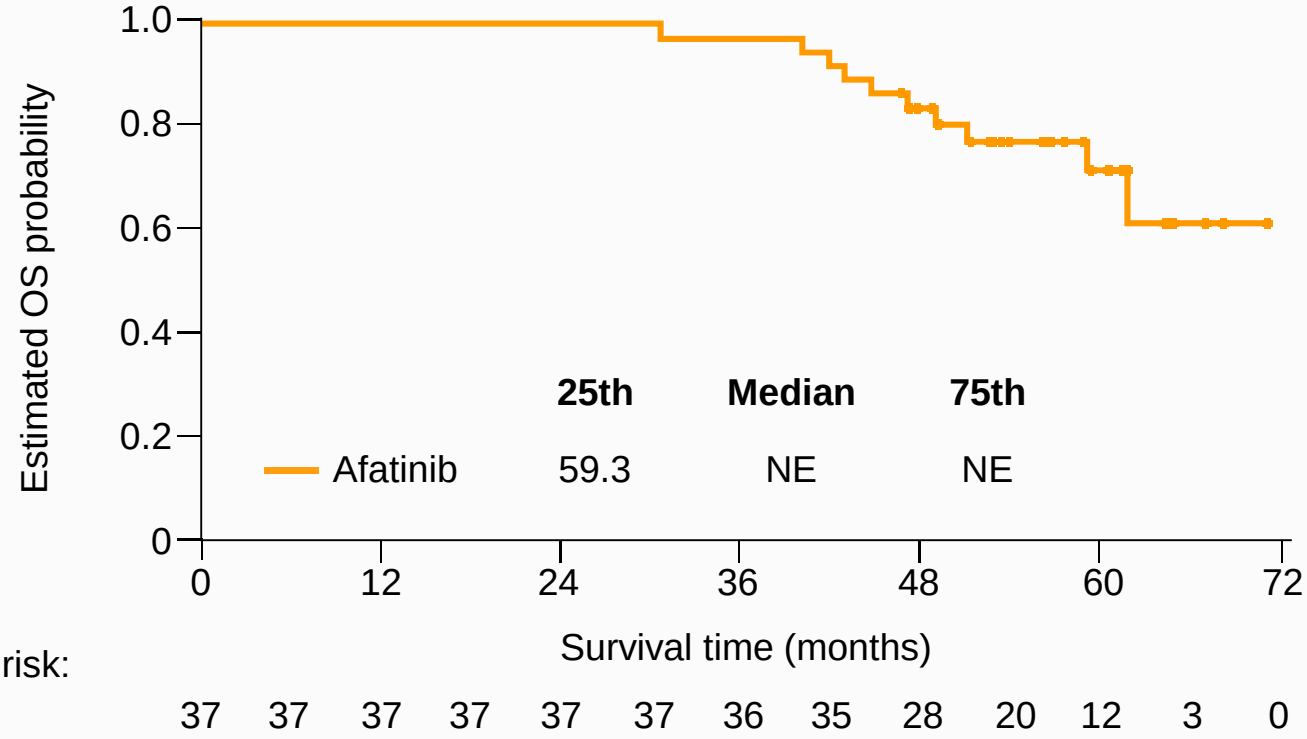



**In 10 patients who received consecutive afatinib and osimertinib, median PFS-2† was 53.3 months (95% CI: 36.9, not reached)**

Data cut-off for LUX-Lung 7: August 2017; *Kaplan–Meier estimate; †Time from initiation of afatinib to the last day of osimertinib therapy.

# Overall survival in patients who received subsequent osimertinib in any treatment line following first-line afatinib

- Most patients who received subsequent osimertinib did so in the ≥third-line setting (n=27)

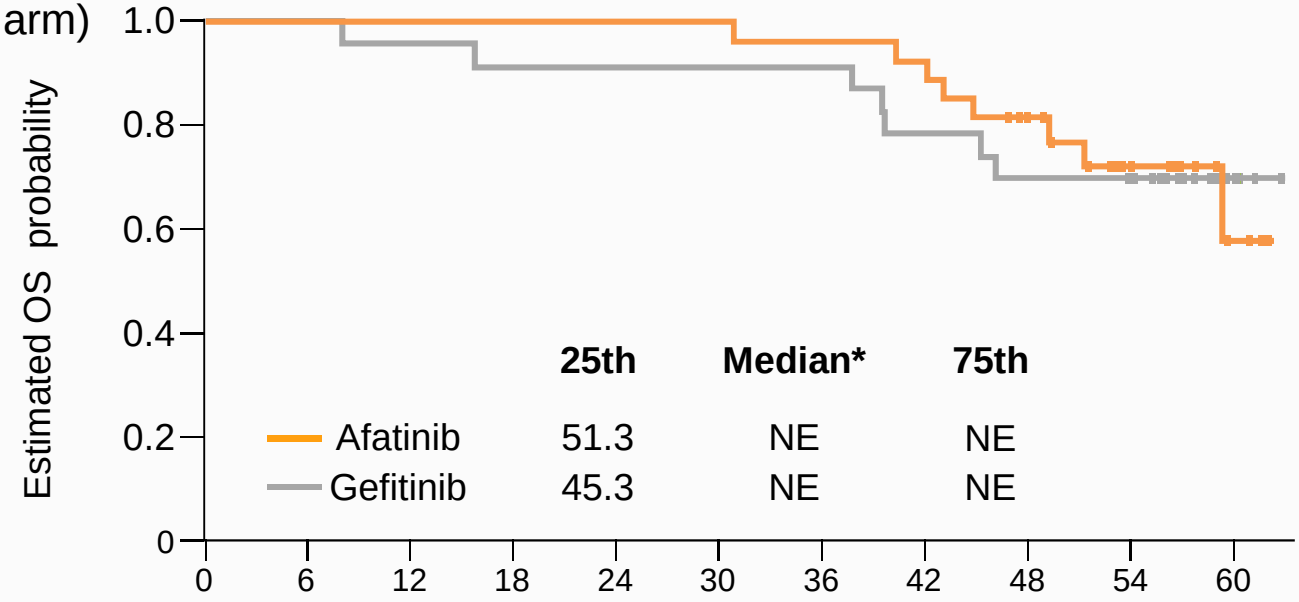



**After a median follow-up of 4.7 years, median OS in patients treated with sequential afatinib and osimertinib had not been reached**

Data cut-off for LUX-Lung 7: August 2017.
NE, not evaluable.

# Overall survival in patients who received osimertinib after afatinib or gefitinib in LUX-Lung 7

- Most patients who received subsequent osimertinib did so in the ≥third-line setting (n=18 in each arm)



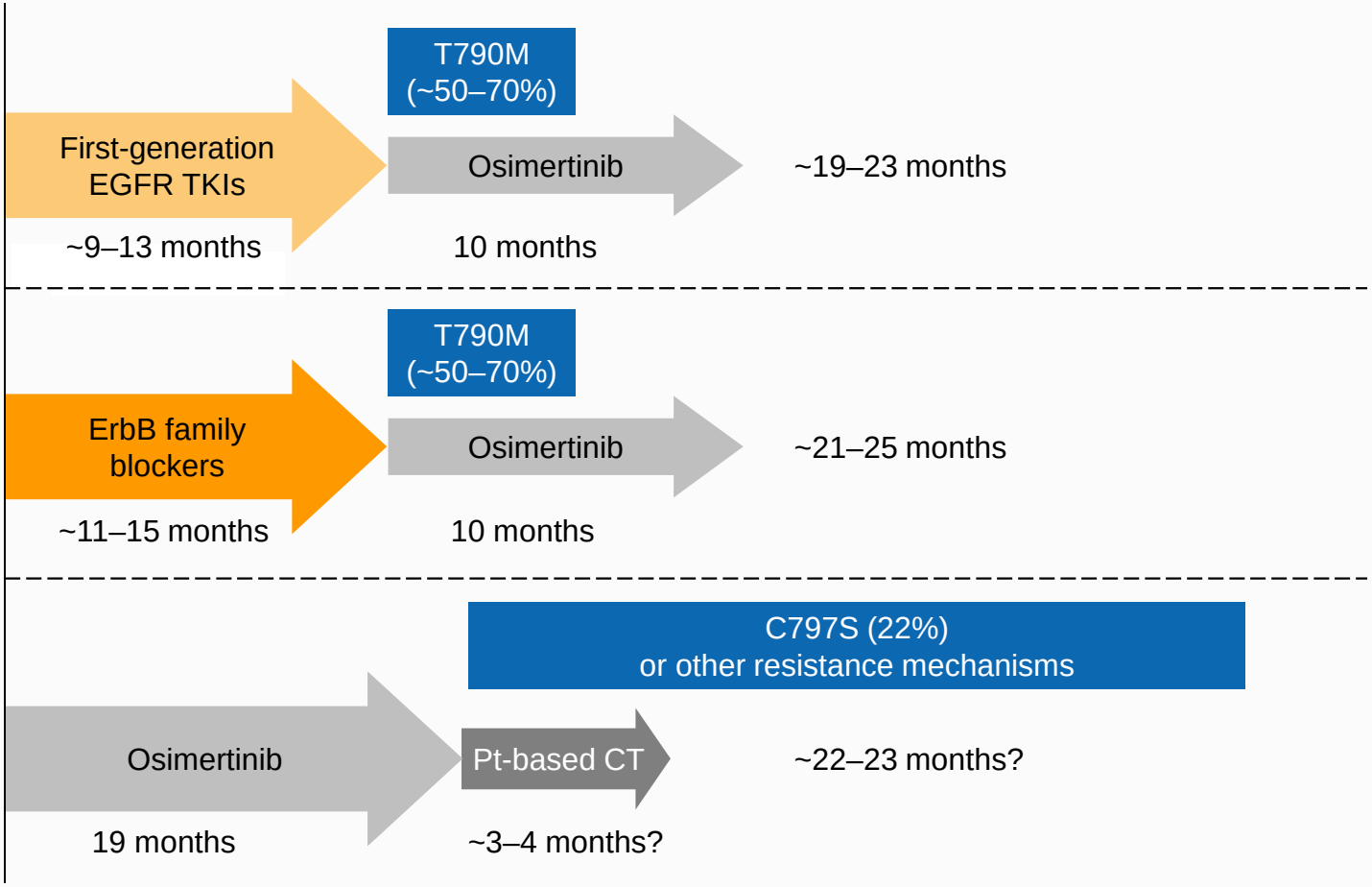

Number at risk:

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Afatinib | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 26 | 26 | 26 | 25 | 22 | 19 | 16 | 11 | 7 | 3 | 0 |
| Gefitinib | 23 | 23 | 23 | 22 | 22 | 22 | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 20 | 18 | 18 | 16 | 16 | 15 | 10 | 4 | 0 |

**Median OS was not reached in either group***

Data cut-off August 2017; *Median follow-up 52.8 months (afatinib) and 56.0 months (gefitinib).

# Possible sequential regimens of EGFR TKIS in patients with EGFR mutation-positive NSCLC




Pt, platinum.

# Discussion

- Most patients (71%) treated with first-line afatinib received subsequent therapies
- No relevant difference was seen in second-line treatment duration between Del19 and L858R mutation subgroups
- First-generation EGFR TKIs were used frequently
- Duration of osimertinib treatment after first-line afatinib was unexpectedly long at 20 months and the OS for the sequence was > 4years
  - This result warrants further examination
- These findings support treatment sequencing with first-line afatinib followed by subsequent therapies, including osimertinib

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- Previously presented: Sequist LV, et al. CSCO 2017; poster #P-26

# Online resources

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