Activity of afatinib in uncommon epidermal growth factor receptor (EGFR) mutations: Findings from three prospective trials of afatinib in EGFR mutation-positive lung cancer

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Conflict of interest disclaimer

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Introduction

- The presence of somatic mutations in *EGFR* influences treatment strategy for patients with NSCLC[1]
- The two most common *EGFR* mutations account for >85% of all mutation-positive NSCLC cases and are known to confer sensitivity to EGFR TKIs:[2]
  - In-frame deletion in exon 19 (Del19)
  - Point mutation in exon 21 (L858R)
- Anecdotal data from erlotinib/gefitinib trials show variable and mainly limited responses to EGFR TKIs in a multitude of other *EGFR* mutations e.g. in exons 18–21 or a combination of ≥2 *EGFR* mutations[3,4]
- To our knowledge, this is the largest series of prospective efficacy data in uncommon mutations are available from the LUX-Lung programme with afatinib[5–7]

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6. Katakami N. et al. J Clin Oncol. 2013;31:3335–41; 7. Wu Y, et al. ASCO 2013; Abstract 8016.

LUX-Lung clinical trials and eligibility

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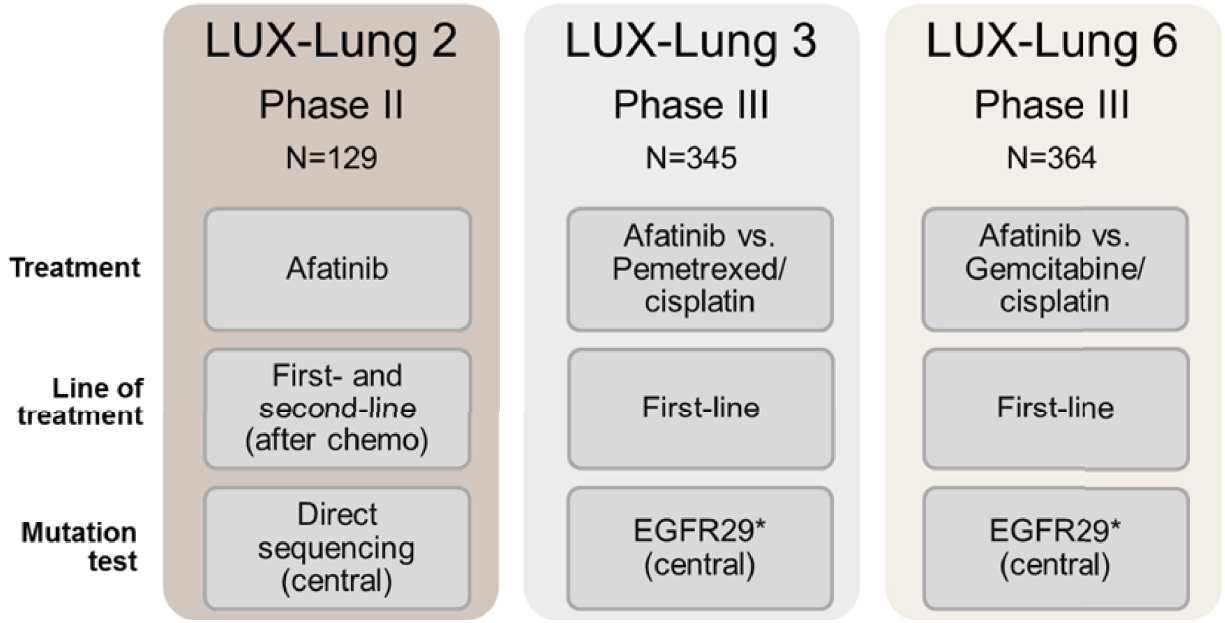
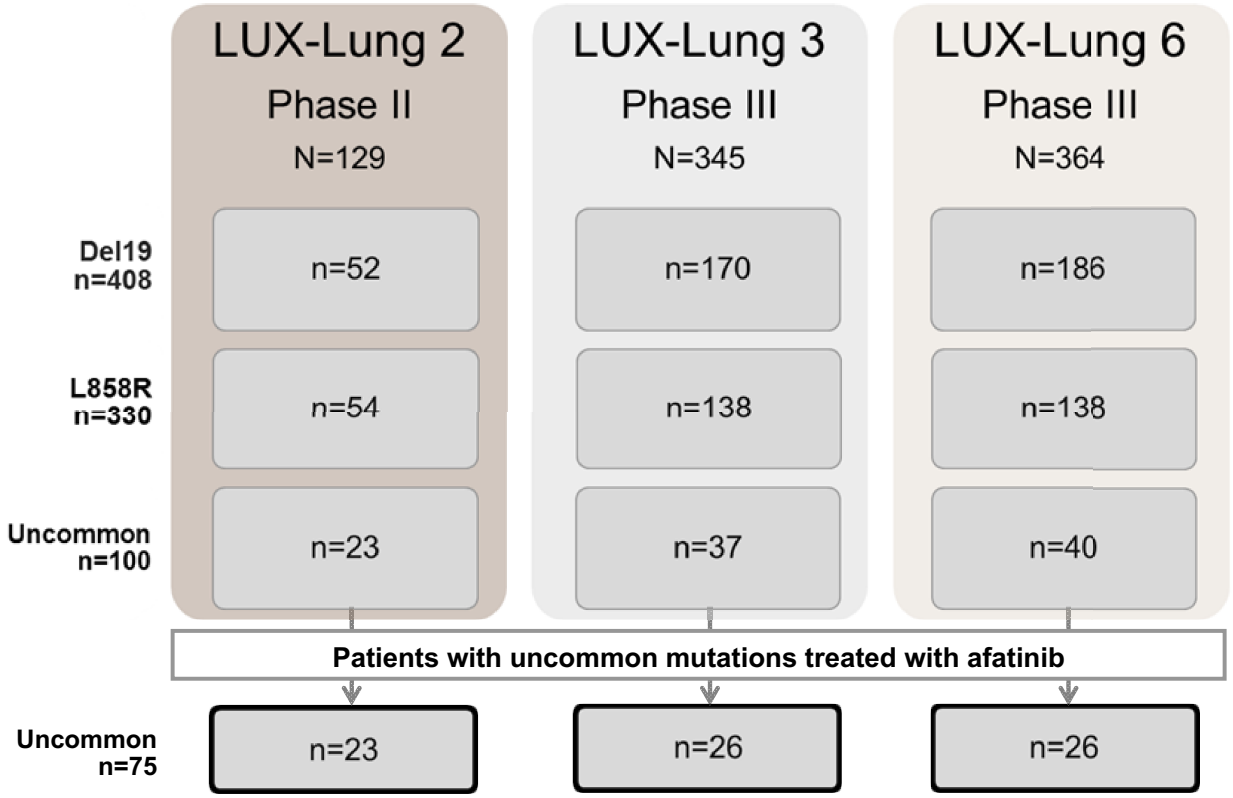


*EGFR mutations detected by TheraScreen EGFR29 test:

- Common: 19 deletions in exon 19 and L858R in exon 21
- Uncommon: 3 insertions in exon 20, L861Q, T790M, G719S, G719A and G719C, S768I

EGFR mutation-positive patients in LUX-Lung trials



Baseline patient characteristics across mutation types

Afatinib- and chemotherapy-treated patients (LUX-Lung 2, 3 and 6)

		Del 19 n=408	L858R n=330	Uncommon n=100
Age, years median (range)		58 (27–84)	61 (32–86)	60 (30–86)
Gender, n (%)	Female	256 (63)	223 (68)	58 (58)
Smoking status, n (%)	Never smoked	288 (71)	242 (73)	68 (68)
	Ex-smoker	98 (24)	75 (23)	28 (28)
	Current smoker	22 (5)	13 (4)	4 (4)
Race, n (%)	Caucasian	54 (13)	39 (12)	14 (14)
	Asian	351 (86)	289 (88)	85 (85)
	Other	3 (1)	2 (1)	1 (1)
Stage (AJCC 6.0), n (%)	IIIB (wet)	33 (8)	31 (9)	3 (3)
	IV	375 (92)	299 (91)	97 (97)
ECOG PS, n (%)	0	150 (37)	112 (34)	43 (43)
	1	257 (63)	214 (65)	57 (57)
	2	1 (<1)	4 (1)	0 (0)

AJCC = American Joint Committee on Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.

Subgroups of patients with uncommon mutations

Categories	*De novo* T790M	Exon 20 insertions	Other (exon 18, 19, 20, 21)
n=	14	23	38
Mutations (n)	T790M alone (3) T790M+Del19 (3) T790M+L858R (6) T790M+G719X (1) T790M+L858R+G719X (1)	n/a	L861Q alone (12) G719X alone (8) G719X+S768I (5) G719X+L861Q (3) E709G or V+L858R (2) S768I+L858R (2) S768I alone (1) L861P alone (1) P848L alone (1) R776H+L858R (1) L861Q+Del19 (1) K739_1744dup6 (1)

Objective response and disease control rates

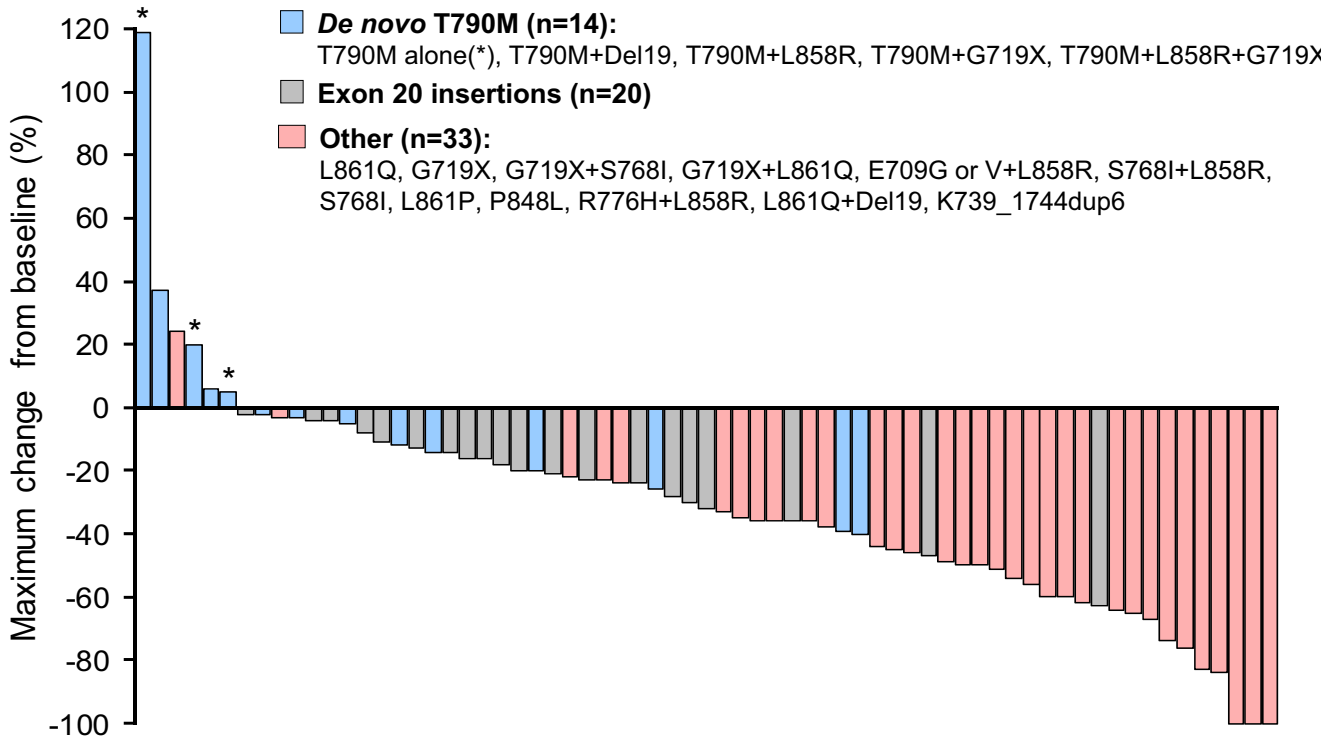
Independent review

	De novo T790M n=14	Exon 20 insertions n=23	Other n=38
Objective response rate (CR + PR), n (%)	2 (14.3%)	2 (8.7%)	27 (71.1%)
Median duration of response, months (range)	8.2 (4.1–12.4)	7.1 (4.2–10.1)	11.1 (1.3–35.0+)
Disease control rate (CR + PR + SD), n (%)	9 (64.3%)	15 (65.2%)	32 (84.2%)

+Patient data censored

Tumour shrinkage in patients with uncommon mutations

Independent review (n=67†)



†8 patients were not included due to insufficient data

Progression-free survival and overall survival in patients

Independent review

	De novo T790M n=14	Exon 20 insertions n=23	Other n=38
Median PFS, months (range)	2.9 (0.3–13.8)	2.7 (0.4-11.9)	10.7 (0.0+-35.8+)
Median OS, months (range)	14.9 (1.5-30.5)	9.4 (0.4-32.2+)	18.6 (0.0+-51.3+)

T790M + L858R, n=6

Patient	PFS	OS
1	0.8	8.7
2	2.6	24.9
3	6.7	13.2
4	8.3	30.5
5	9.6*	24.4*
6	11.0	20.8
Median	**7.5**	**22.9**

T790M + Del19, n=3

Patient	PFS	OS
1	0.3	8.1
2	1.2	7.5
3	3.0	24.6
Median	**1.2**	**8.1**

+Patient data censored; NE = not estimable

Activity of afatinib in specific uncommon EGFR mutations

Genotypes		ORR, n (%)	PFS (months), median (95% CI)	OS (months), median (95% CI)
G719X (n=18)	G719X (n=8) G719X+T790M (n=1) G719X+S768I (n=5) G719X+L861Q (n=3) G719X+T790M+L858R (n=1)	14 (78)	13.8 (6.8–NE)	26.9 (16.4–NE)
L861Q (n=16)	L861Q (n=12) L861Q+G719X (n=3) L861Q+Del19 (n=1)	9 (56)	8.2 (4.5–16.6)	16.9 (15.3–22.0)
S768I (n=8)	S768I (n=1) S768I + G719X (n=5) S768I +L858R (n=2)	8 (100)	14.7 (2.6–NE)	NE (3.4–NE)

Note: A patient may be presented in more than one category

NE = not estimable

Summary

- Largest prospective dataset in patients with uncommon *EGFR* mutations (n=75)
- High heterogeneity within the subgroup with uncommon EGFR mutations
- Low response rate in patients with exon 20 insertions and T790M tumours
  - Durable tumour control observed in some cases (PFS up to 13.8 months)
- Activity was observed in other exon 18 (G719X), 20 (S768I) and 21 (L861Q) mutations that are known to be less responsive to reversible EGFR TKIs
  - Activity was in the range of efficacy observed with afatinib in common *EGFR* mutations