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Afatinib in EGFR TKI-naïve patients with *EGFR* mutation-positive (*EGFR*m+) NSCLC: interim analysis of a Phase IIIb, multi-national, open-label study

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Introduction

- Afatinib, an irreversible ErbB family blocker, demonstrated significantly improved efficacy outcomes and a manageable safety profile in patients with *EGFR*m+ NSCLC when compared with platinum-doublet chemotherapy in Phase III clinical trials[1,2]

LUX-Lung 3 (Global) and 6 (China, South Korea and Thailand)

- Median PFS with first-line afatinib versus platinum-doublet chemotherapy in patients with *EGFR*m+ NSCLC:
  - LUX-Lung 3: 11.1 vs 6.9 months, HR=0.58; p=0.001[1]
  - LUX Lung 6: 11.0 vs 5.6 months, HR=0.28; p<0.0001[2]

- These findings led to the approval of afatinib in many countries for the first-line treatment of patients with *EGFR*m+ NSCLC[3,4]
- As RCTs are conducted in highly controlled settings, with strict inclusion criteria, it is important to support findings of afatinib efficacy and tolerability with real-world studies of broader patient populations

*EGFR*m+, epidermal growth factor receptor mutation-positive; HR, hazard ratio; PFS, progression-free survival; RCT, randomised controlled trial

Objectives

- The aim of this prospective study, 1200.55 (NCT01853826), was to evaluate the efficacy and safety of afatinib in *EGFR*m+ NSCLC, in a patient population similar to real-world practice

Methods

Global, prospective, open-label, single-arm, multicentre, Phase IIIb study

Key inclusion criteria	• Locally advanced or metastatic *EGFR*m+ NSCLC • EGFR TKI-naïve • ECOG PS 0–2 • Patients with asymptomatic brain metastases were permitted*
Key exclusion criteria	• Prior EGFR TKI treatment
Treatment	• Afatinib 40 mg/day until disease progression or other withdrawal criteria were met • Dose reduction in 10-mg decrements to a minimum of 20 mg/day was permitted
Primary endpoint†	• Safety assessment (AEs measured descriptively)
Further endpoints	• TTSP • PFS • ORR (CR+PR) • DCR (CR+PR+SD)

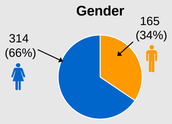
*Previously treated, with SD for ≥4 weeks on stable doses of medication; †Disease assessments and AEs recorded at baseline and every 28 days during treatment. All patients who received ≥1 dose of afatinib (treated set) were included in safety and efficacy analyses
AE, adverse event; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTSP, time to symptomatic progression

Baseline characteristics

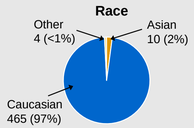
Interim analysis
Data cut-off: April 2018

N=479
patients enrolled and treated

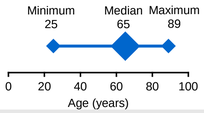
Gender

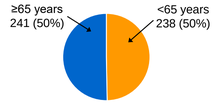


Race



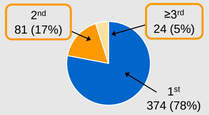
Age



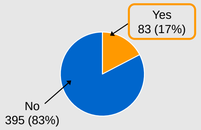


The study population included patients who are sometimes not eligible for RCTs[1,2,5]

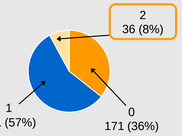
Line of therapy



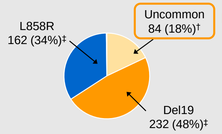
Brain metastases*



ECOG PS*



EGFR* mutation type



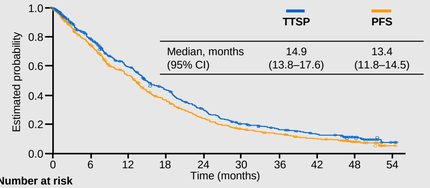
	n (%)§
ex20ins	37 (8)
G719S/A/C	12 (3)
T790M	12 (3)
L861Q	10 (2)
S768I	9 (2)
Other	18 (4)

Percentages may not total 100% due to rounding
*Missing (n=1); †Uncommon *EGFR* mutations with/without common mutations (uncommon mutations only, n=62); ‡Del19 or L858R mutations only (i.e., no uncommon mutations); §Patients can appear in more than one mutation category

Efficacy

- Overall efficacy outcomes were encouraging in this broad patient population (Figures 1 and 2)

Figure 1. Median TTSP and PFS (N=479)

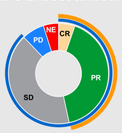


	TTSP	PFS
Median, months (95% CI)	14.9 (13.8–17.6)	13.4 (11.8–14.5)

Number at risk

TTSP	479	332	237	167	113	72	55	41	21	2
PFS	479	332	229	151	98	67	51	36	16	1

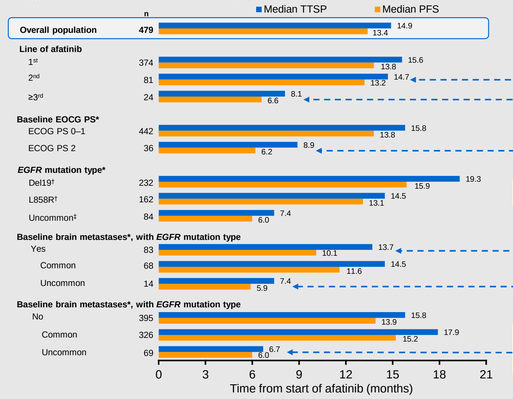
Figure 2. Best tumour response



ORR 46% (n=218)
DCR 86% (n=411)

Best tumour response (N=479)	n (%)
CR	25 (5)
PR	193 (40)
SD	193 (40)
PD	34 (7)
NE	23 (5)

Figure 3. Median TTSP and PFS by patient subgroup



*Missing n=1; †Del19 or L858R mutations only (i.e., no uncommon mutations); ‡Uncommon *EGFR* mutations with/without common mutations
CI, confidence interval; NE, not evaluable; PD, progressive disease

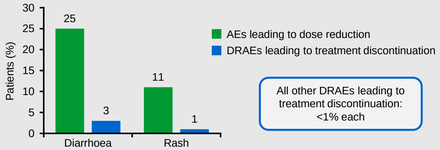
- Clinical benefit was demonstrated across a range of subgroups (Figure 3)
- As also observed in the LUX-Lung trials,[1,2,5] prolonged efficacy was seen in patients with ECOG PS 0/1, and in patients with Del19+ NSCLC
- Afatinib demonstrated efficacy in hard-to-treat patient subgroups, including those sometimes excluded from clinical trials[1,2,5]
- The lower efficacy in the uncommon mutation subgroup may be due to the relatively high proportion of exon 20 insertions in this group[6]
- Outcomes according to specific type of uncommon *EGFR* mutation type will be further evaluated

Safety

- AEs were predictable and manageable, and were consistent with results of RCTs[1,2,5]
  - 462 (96%) patients had at least one DRAE (Table 1), most commonly diarrhoea and rash
  - These were also the most common AEs leading to dose reduction, but led to few discontinuations (Figure 4)

40 mg/day → n=258 (54%)* → 30 mg/day → n=87 (18%)* → 20 mg/day

Figure 4. Most common AEs leading to dose reduction and DRAEs leading to treatment discontinuation



All other DRAEs leading to treatment discontinuation: <1% each

*Percentage of overall population (N=479); †DR SAEs n=39 (8%), most commonly diarrhoea n=15 (3%), dehydration n=6 (1%), vomiting n=5 (1%), all others n<4 (<1%) each. DRAE, drug-related adverse event; DR SAE, drug-related serious adverse event; SAE, serious adverse event

Table 1. Summary of AEs

	All grades, n (%)	Grade ≥3, n (%)
Any AE	478 (>99)	315 (66)
Any SAE†	202 (42)	171 (36)
AE leading to dose reduction	258 (54)	156 (33)
Any DRAE	462 (96)	210 (44)
DRAE leading to treatment discontinuation	37 (8)	26 (5)
DRAEs in ≥10% of patients		
Diarrhoea	416 (87)	77 (16)
Rash	246 (51)	51 (11)
Paronychia	142 (30)	17 (4)
Mucosal inflammation	87 (18)	12 (3)
Dry skin	79 (16)	1 (<1)
Stomatitis	67 (14)	8 (2)
Skin fissures	51 (11)	3 (<1)
Nausea	50 (10)	5 (1)
Conjunctivitis	50 (10)	3 (<1)
Dermatitis acneiform	49 (10)	8 (2)

Key findings and conclusions

- Interim efficacy and safety results with afatinib in this near 'real-world' patient population with *EGFR*m+ NSCLC are consistent with findings from the pivotal LUX-Lung trials[1,2,5]
  - Median TTSP and PFS in the overall population were 14.9 and 13.4 months, respectively. Prolonged efficacy was seen in patients with ECOG PS 0/1 and patients with Del19+ NSCLC
  - Diarrhoea and rash were the most common DRAEs. Both were generally manageable with dose reduction and led to few treatment discontinuations
- Importantly, afatinib also demonstrated clinical benefit in patients who are sometimes excluded from clinical trials, such as those with ECOG PS 2, asymptomatic brain metastases, NSCLC harbouring uncommon *EGFR* mutations, and those who received ≥1 previous line of therapy

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