AFATINIB IN EGFR TKI-NAÏVE PATIENTS WITH LOCALLY ADVANCED/METASTATIC NSCLC HARBOURING *EGFR* MUTATIONS: AN INTERIM ANALYSIS OF A PHASE IIIB TRIAL

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Background

- EGFR TKIs are the first-line standard of care for patients with *EGFR*m+ NSCLC[1]
- Afatinib, a second-generation ErbB family blocker, irreversibly blocks signalling from all relevant homo- and heterodimers formed by ErbB receptor family members (ErbB1–4)[2]
- In the Phase III LUX-Lung 3 and 6 studies, first-line afatinib significantly improved PFS and ORR versus platinum-doublet chemotherapy in patients with *EGFR*m+ NSCLC, as well as OS in those with Del19+ disease, while demonstrating a manageable safety profile[3–5]
- Furthermore, in the Phase IIb LUX-Lung 7 study, afatinib significantly improved PFS, ORR and TTF versus the first-generation EGFR TKI gefitinib[6]

RCTs are conducted in highly controlled settings with strict inclusion criteria[3,4,6]; therefore, it is important to assess whether clinical trial outcomes are reflected in the real-world treatment setting

*EGFR*m+, *EGFR* mutation-positive; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TKI, tyrosine kinase inhibitor; TTF, time-to-treatment failure

1. Bulbul A, Husain H. Front Oncol 2018;8:94. 2. Girard N. Future Oncol 2018;14:1117–32. 3. Sequist L, et al. J Clin Oncol 2012;31:3327–34. 4. Wu YL, et al. Lancet Oncol 2014;10:S1470–45. 5. Yang JC, et al, Lancet Oncol 2015;16:141-51. 6. Park K, et al. Lancet Oncol 2016;17:577–89.

Interim Analysis of an Open-label, Multicentre, Phase IIIb Trial

- Patients with locally advanced/metastatic *EGFR*m+ NSCLC
- EGFR TKI-naïve
- ECOG PS 0–2
- Patients with asymptomatic brain metastases permitted

Afatinib 40 mg/day until disease progression or other withdrawal criteria were met

Dose reduction to 30 or 20 mg/day was permitted based on individual tolerability

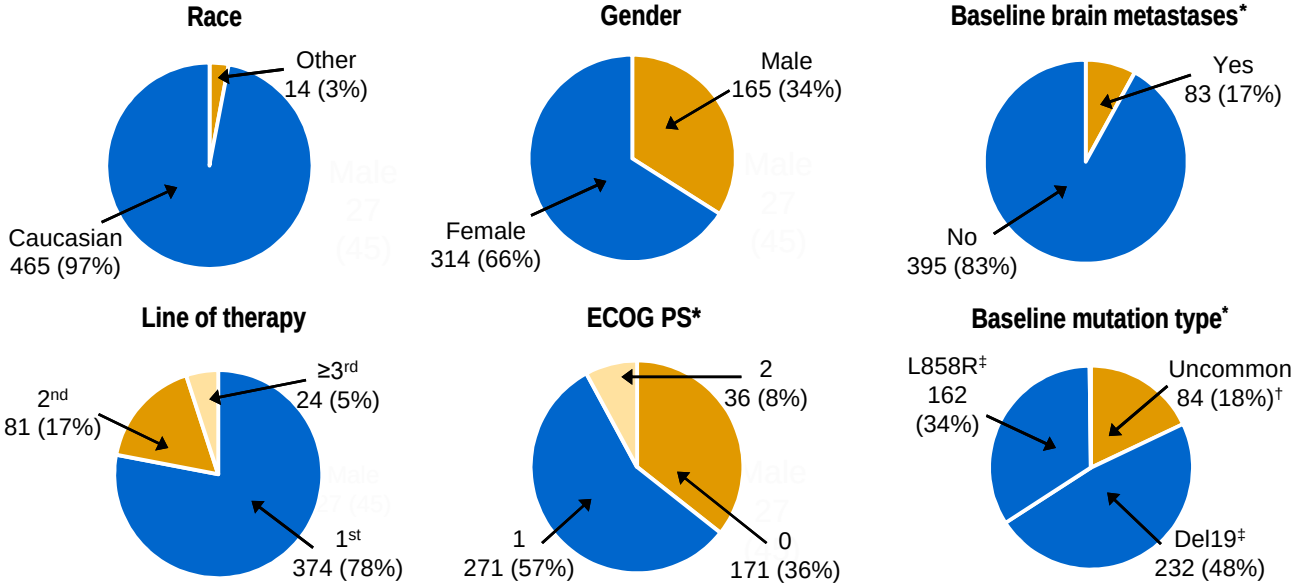
Primary endpoint: Safety (AEs in descriptive fashion)
Efficacy endpoints: PFS, TTSP, ORR, DCR

- AEs were recorded at baseline and then every 28 days during treatment. Physical examinations and disease assessments were performed at the same time points
- All patients who received at least one dose of afatinib (treated set) were included in the safety and efficacy analysis

AEs, adverse events; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; TTSP, time to symptomatic progression

Patient Disposition and Baseline Characteristics

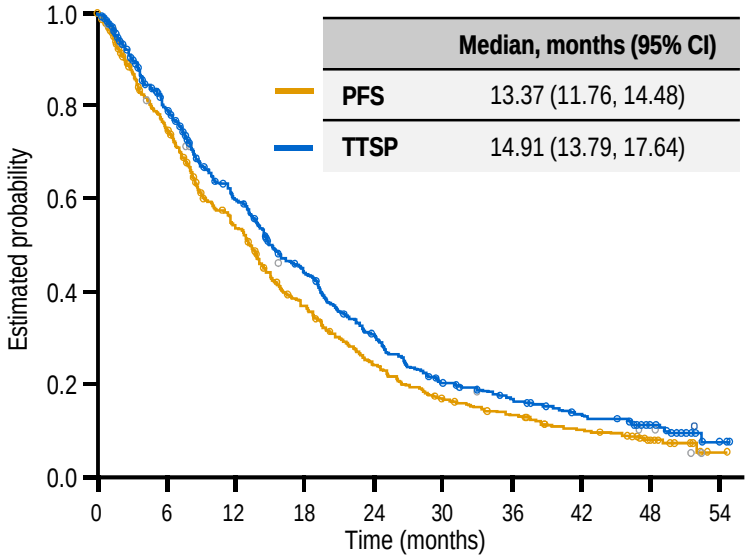
- 479 patients were treated and included in this interim analysis



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

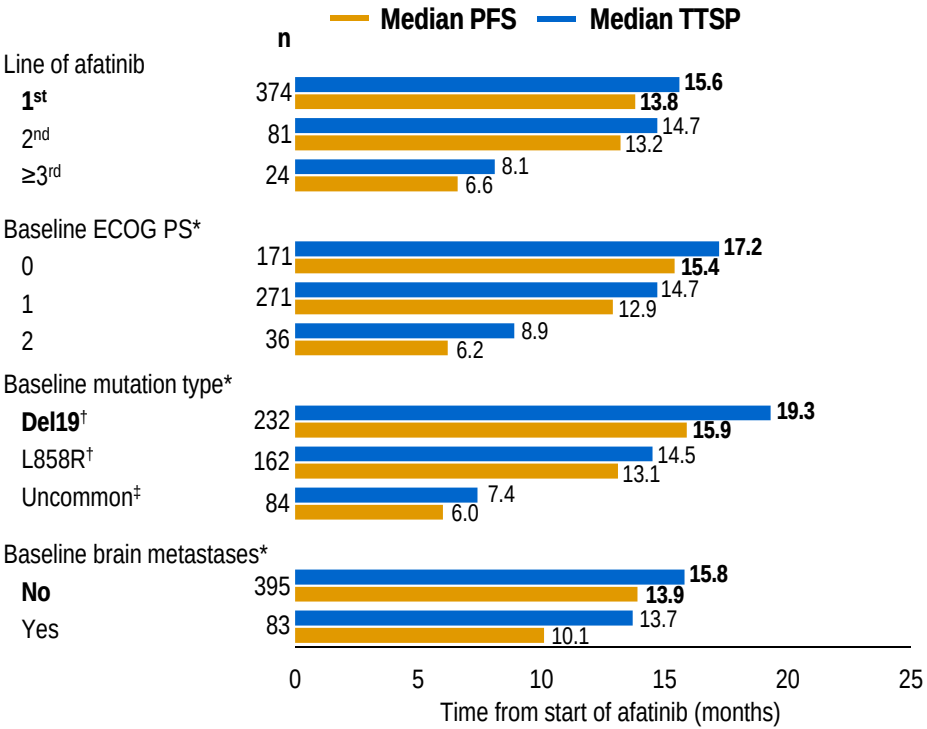
*Missing (n=1); †Uncommon *EGFR* mutations with/without common mutations (uncommon mutations only, n=62);
‡Del19 or L858R mutations only (i.e., no uncommon mutations)
Data cut-off: 30 April 2018

PFS and TTSP



Number at risk

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

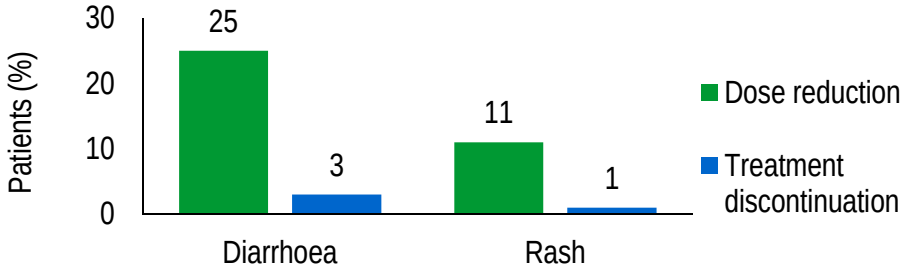


*Missing n=1; †Del19 or L858R mutations only (i.e., no uncommon mutations); ‡Uncommon *EGFR* mutations with/without common mutations;
Overall ORR breakdown, n (%): CR: 25 (5.2); PR: 193 (40.3); SD: 193 (40.3)
CI, confidence interval

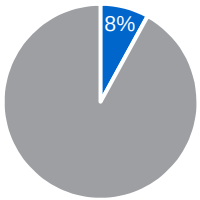
AEs were Predictable and Manageable

Most common TRAEs (≥10%), n (%)		
	All grades	Grade ≥3
Diarrhoea	416 (87)	77 (16)
Rash	246 (51)	51 (11)
Paronychia	142 (30)	17 (4)
Mucosal inflammation	87 (18)	12 (3)
Dry skin	79 (17)	1 (0.2)
Stomatitis	67 (14)	8 (2)
Skin fissures	51 (11)	3 (0.6)
Nausea	50 (10)	5 (1)
Conjunctivitis	50 (10)	3 (0.6)
Dermatitis acneiform	49 (10)	8 (1.7)

258 (54%) patients had AEs leading to dose reduction (to 30 mg, n=258 [54%]; 20 mg, n=87 [18%])
The most common of these AEs were diarrhoea and rash:



37 (8%) patients had TRAEs leading to treatment discontinuation, most commonly diarrhoea (3%)



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

TRAE, treatment-related AE

Conclusions

- In this interim analysis from a large Phase IIIb study, the patient population was reflective of real-world treatment practice
  - 22% of patients were treated with afatinib as ≥2nd line therapy, 8% had an ECOG PS of 2, 17% had brain metastases and 18% had uncommon *EGFR* mutations
  - Insertions in exon 20 were the most frequently observed type of uncommon *EGFR* mutation (8%)
- Overall, the interim safety and efficacy results were consistent with those observed for afatinib in the LUX-Lung 3, 6 and 7 trials[1–3]
  - Afatinib showed a predictable and manageable safety profile
  - Afatinib-related AEs led to treatment discontinuation in 8% of patients
  - Efficacy findings were also encouraging, with an overall median PFS and TTSP of 13.4 and 14.9 months, respectively
    - Activity of afatinib in patients with brain metastases was confirmed (median PFS 10.1 months; median TTSP 13.7 months)

1. Sequist L, et al. J Clin Oncol 2012;31:3327–34. 2. Wu YL, et al. Lancet Oncol 2014;10:S1470–45.
3. Park K, et al. Lancet Oncol 2016;17:577–89.

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