A Phase IIIb trial of afatinib in *EGFR* m+ NSCLC: analysis of outcomes in patients with brain metastases or dose reductions

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Introduction

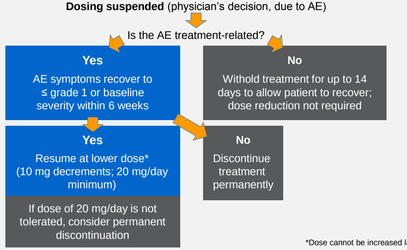
- Afatinib, an irreversible second-generation ErbB family blocker, is approved in many countries for first-line treatment of patients with advanced *EGFR* mutation-positive (*EGFR* m+) NSCLC
- We reported interim results of a large open-label, single-arm Phase IIIb study (NCT01953913) of afatinib in EGFR TKI-naïve patients with *EGFR* m+ NSCLC, in conditions similar to 'real-world' clinical practice[1]
  - broad population of Asian patients
  - predictable and manageable tolerability profile
  - adverse events (AEs) consistent with the LUX-Lung 3, 6 and 7 trials;[2–4] 4% of patients discontinued due to treatment-related AEs
  - Progression-free survival (PFS) and time to symptomatic progression (TTSP†) was encouraging in patients with both common and uncommon *EGFR* mutations
  - TTSP data suggested effective treatment beyond progression
- Here we assess the impact of baseline brain metastases on efficacy outcomes, and the effect of dose reductions on efficacy, safety and tolerability

†Time from first administration of afatinib to date of first documented clinically significant symptomatic progression requiring a change in or stopping of anti-cancer treatment, as assessed by the investigators.

Methods

- Objective: To evaluate the safety of afatinib in patients with locally advanced or metastatic NSCLC harboring *EGFR* mutation(s) who have never been treated with an EGFR TKI
- The study design was previously reported[1]
  - Patients (N=479) received afatinib 40 mg (orally, once daily) until investigator-assessed tumor progression or lack of tolerability
  - Objectives: primary, safety; secondary, TTSP, PFS
  - Formal statistical tests were not specified in the analysis plan

Tolerability-guided treatment interruptions / dose adjustments



*Dose cannot be increased later.

Baseline characteristics (N=479)

Country	Patients, n (%)
China	351 (73)
India	50 (10)
Taiwan	29 (6)
Hong Kong	25 (5)
Singapore	24 (5)

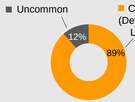
Age at baseline, years

Min. 27 | Median 59 | Max. 82

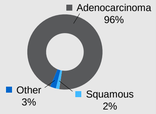
<65 years: 74% | ≥65 years: 26%

Gender

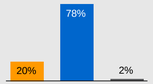
***EGFR* mutation type**



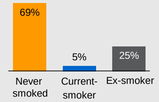
Tumor histology



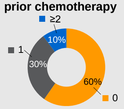
ECOG PS



Smoking history



Number of lines of prior chemotherapy



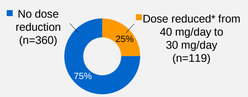
*With or without an uncommon EGFR mutation.
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

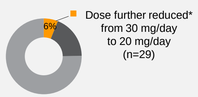
Patients with AEs leading to dose reduction (N=479)

AE, n (%)	≥ grade 3	Any grade
Diarrhea	24 (5.0)	47 (9.8)
Rash/acne[a]	34 (7.1)	41 (8.6)
Stomatitis[a]	15 (3.1)	22 (4.6)
Paronychia[a]	12 (2.5)	13 (2.7)

AEs leading to a dose reduction (any grade) in >1% of patients. [a]Grouped term. AEs were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events ver 3.0. AE, adverse event.

Use of dose reductions with afatinib: frequency and impact on efficacy outcomes





Duration of treatment, months

Min. 0.2 | Median 9.7 | Max. 38.6

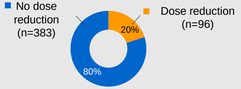
Time to first dose reduction, months

Min. 0.2 | Median 1.5 | Max. 27.6

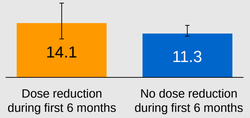
Data are %. *At any time during the study

- The use of dose reduction during the first 6 months of the study had no negative impact on PFS and TTSP

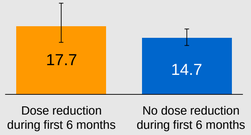
Dose reductions during first six months



Median PFS, months (95% CI)



Median TTSP, months (95% CI)

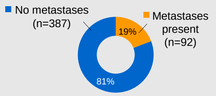


CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TTSP, time to symptomatic progression.

Presence of brain metastases* at baseline: frequency and impact on efficacy outcomes

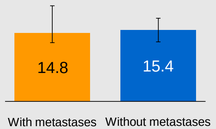
- PFS was numerically shorter in patients with brain metastases at baseline than in those without
- There was no notable difference in TTSP between the two subgroups

Brain metastases* at baseline



Median PFS, months (95% CI)

Median TTSP, months (95% CI)



*Asymptomatic
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TTSP, time to symptomatic progression.

Impact of dose reductions on safety and tolerability

- The most frequently reported TRAEs[a] (any grade and ≥ grade 3) were substantially reduced following tolerability-guided dose reduction

TRAE, %	Before dose reduction		After dose reduction	
	≥ grade 3	Any grade	≥ grade 3	Any grade
Diarrhea	26.1	95.8	4.2	51.3
Rash/acne[b]	24.4	68.9	10.9	58.0
Stomatitis[b]	10.9	63.0	5.0	40.3
Paronychia[b]	8.4	37.8	3.4	46.2
Dry skin	0.8	12.6	0[c]	4.2
Decreased appetite	0.8	10.9	0.8	4.2
Vomiting	1.7	10.1	0[c]	5.0

[a]TRAEs occurring (at any grade) in >10% of patients prior to dose reduction (based on 119 patients who had a dose reduction at any time during the study), evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events ver 3.0. [b]Grouped term. [c]no patients with TRAE. TRAE, treatment-related adverse event.

Key findings and conclusions

- This analysis provides additional evidence for the efficacy of afatinib in *EGFR* m+ NSCLC patients with brain metastases
  - PFS was shorter in patients with brain metastases at baseline (10.9 months) than those without (12.4 months) but TTSP was similar (14.8 versus 15.4 months, respectively)
- Use of tolerability-guided dose adjustment, when required, may ameliorate TRAEs with afatinib and maintain therapeutic efficacy
  - The frequency of commonly occurring TRAEs was reduced following dose reductions (and overall, only 4% of patients discontinued afatinib due to TRAEs)[1]
  - The efficacy of afatinib was not compromised by the use of dose reductions in the first six months; median PFS was 14.1 months in patients who had a dose reduction, and 11.3 months in those who remained on 40 mg/day; TTSP was also longer in patients who had a dose reduction
    - These findings should be viewed with caution, as the study was not controlled; plus, only 96 patients had a dose reduction, versus 383 who did not

References

1. Wu Y-L, et al. J Thorac Oncol 2017;12:S2214
2. Sequist LV, et al. J Clin Oncol 2013;31:3327–34
3. Wu Y-L, et al. Lancet Oncol 2014;15:213–22
4. Park K, et al. Lancet Oncol 2016;17:577–89

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