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A Phase IIIb open-label study of afatinib in EGFR TKI-naïve patients with *EGFR*m+ NSCLC: Exploratory biomarker analysis

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Introduction

- The safety and efficacy of afatinib, an irreversible second-generation ErbB family blocker, in patients with *EGFR*m+ NSCLC has been demonstrated in Phase III clinical studies,[1,2] and afatinib is now approved for this indication in the majority of countries worldwide
- This Phase IIIb study (NCT01953913) was performed to provide evidence from a near 'real-world' treatment setting on the safety and efficacy of afatinib in EGFR TKI-naïve *EGFR*m+ Asian patients with locally advanced or metastatic NSCLC[3]
- An interim analysis found an afatinib-related SAE rate of 6.1%, with 3.8% of patients discontinuing due to afatinib-related SAEs, suggesting that afatinib-related AEs were manageable. Median TTSP was 15.3 months and median PFS was 12.1 months, suggesting that afatinib may be continued beyond radiological progression[3]
- The final results of this study are presented elsewhere at this conference (Poster #xxxxx)[4]
- Tumour biomarker analysis is increasing in importance as a method of guiding treatment decisions, and has become routine clinical practice. However, more information is needed on how mutations change over the course of treatment in patients with *EGFR*m+ NSCLC. In addition, the role of non-*EGFR* mutations in influencing treatment efficacy and outcomes needs to be elucidated

AE, adverse event; *EGFR*m+, *EGFR* mutation-positive; NSCLC, non-small cell lung cancer; PFS, progression-free survival; SAE, serious adverse event; TKI, tyrosine kinase inhibitor; TTSP, time to symptomatic progression

Objectives

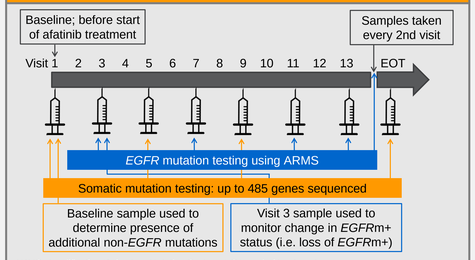
- The aim of this biomarker sub-study was to explore the relationship between tumour mutation type and patients' response to afatinib in terms of efficacy and tolerability

Methods

- In this Phase IIIb trial with a similar setting to 'real-world' practice, EGFR TKI-naïve patients with locally advanced/metastatic *EGFR*m+ NSCLC were recruited from centres in China, Hong Kong, India, Singapore and Taiwan and received afatinib 40mg/day until investigator-assessed progression or lack of tolerability[3]
- The afatinib dose could be reduced to 30 mg/day or 20 mg/day based on pre-defined criteria to manage tolerability
- This biomarker analysis was conducted on patients entering the study at Beijing Cancer Hospital, China, only
- DNA was extracted from peripheral blood (10 mL) taken during scheduled visits (see Figure)
- Analyses of TTSP and PFS were conducted in subgroups by age, ECOG PS, and *EGFR* mutation type at study entry
- PFS was analysed by change in mutation status at Visit 3 and the presence of additional, non-*EGFR* mutations at baseline (see Figure)

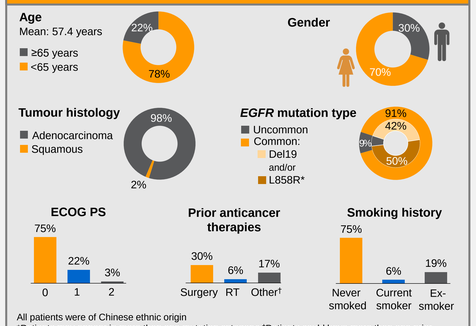
ECOG PS, Eastern Cooperative Oncology Group Performance Status

Methods – biomarker analyses



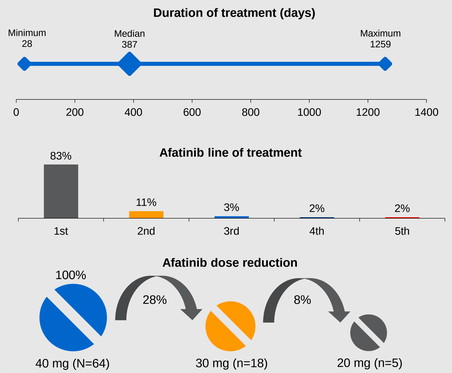
ARMS, Amplification Refractory Mutation System; EOT, end of treatment

Baseline characteristics (N=64)

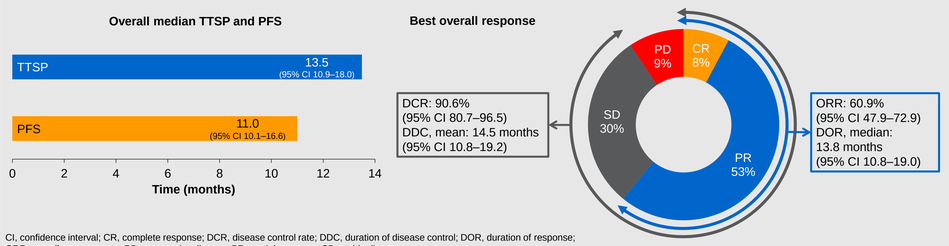


All patients were of Chinese ethnic origin
*Patients may appear in more than one mutation category; †Patients could have more than one prior therapy recorded; ECOG PS, Eastern Cooperative Oncology Group Performance Status; RT, radiotherapy

Treatment exposure

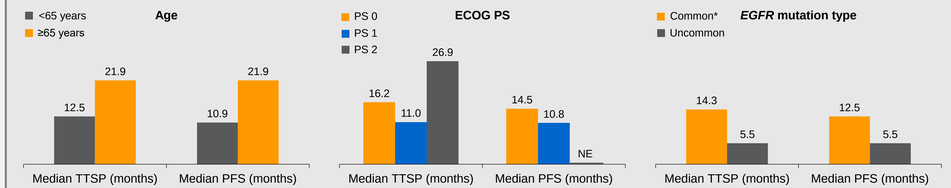


Overall efficacy in biomarker analysis patients (N=64)



CI, confidence interval; CR, complete response; DCR, disease control rate; DDC, duration of disease control; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

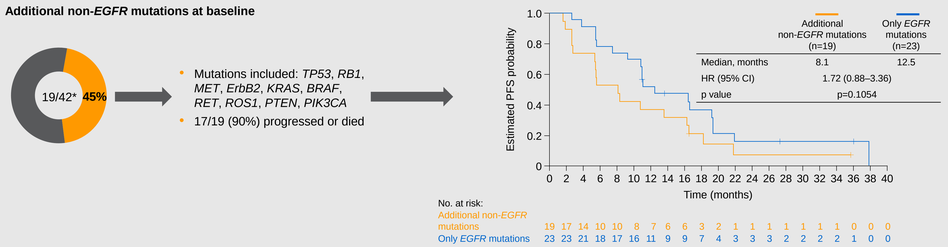
Efficacy by subgroup



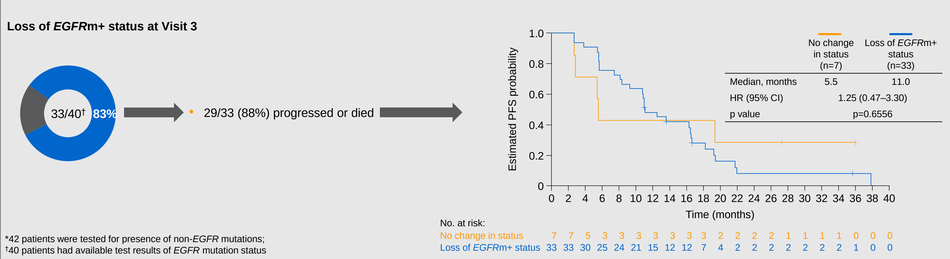
*Del19/L858R; NE, not evaluable

Biomarker analysis

Additional non-*EGFR* mutations at baseline



Loss of *EGFR*m+ status at Visit 3



*42 patients were tested for presence of non-*EGFR* mutations; †40 patients had available test results of *EGFR* mutation status

Safety (N=64)

n (%)	Afatinib 40 mg/day All grades	Grade 3	Grade 4	Grade 5
Any AE	64 (100)	24 (38)	3 (5)	4 (6)*
AE leading to dose reduction	16 (25)	-	-	-
AE leading to treatment discontinuation	7 (11)	-	-	-
SAE	15 (23)†	-	-	-
TRAEs in ≥20% of patients				
Total with TRAE	64 (100)	19 (30)	2 (3)	1 (2)
Diarrhoea	63 (98)	9 (14)	0	0
Rash/acne‡	52 (81)	5 (8)	0	0
Stomatitis‡	46 (72)	1 (2)	0	0
Paronychia‡	32 (50)	4 (6)	0	0
ALT increased	19 (30)	0	0	0
Nasal dryness	15 (23)	0	0	0

*Cancer progression alone (n=1); cancer progression and lung infection (n=1); metastases to CNS (n=1). These were not considered related to afatinib. One death due to decreased appetite was considered treatment related; †Most common SAEs were cerebral infarction (n=3, 5%), malignant neoplasm progression, CNS metastases (both n=2, 3%). The remaining SAEs occurred in single patients only; ‡Grouped terms. ALT, alanine aminotransferase; CNS, central nervous system; TRAE, treatment-related adverse event

Key findings and conclusions

- This exploratory sub-study of a Phase IIIb trial included 64 EGFR TKI-naïve Chinese patients with *EGFR*m+ NSCLC who received afatinib in a near 'real-world' setting
  - 45% of the patients assessed had *EGFR*m+ NSCLC with additional non-*EGFR* mutations at baseline. There was no significant difference in PFS in these patients compared with patients who had NSCLC with only *EGFR* mutations at baseline
  - 83% of the patients assessed had a change of NSCLC mutation status at Visit 3, to *EGFR* mutation-negative. Median PFS was twice as long in these patients compared with patients whose disease remained *EGFR*m+; however, the difference was not statistically significant
- Overall efficacy and safety findings in this subset of Chinese patients were consistent with results from the total Phase IIIb study population (Poster #TBC)[4] and pivotal randomised controlled trials of afatinib[1,2]
  - In this sub-study, clinical benefit was also demonstrated across all subgroups assessed

References

1. Sequist LV, et al. J Clin Oncol 2013;31:3327–34
2. Wu Y-L, et al. Lancet Oncol 2014;15:213–22
3. Wu Y-L, et al. J Thorac Oncol 2017;12:S2214; (Poster P3.01-036)
4. Wu Y-L, et al. Presented at WCLC 2019 (poster #TBC)

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