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[3,4]
- 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[5]
- An interim analysis of 541 patients showed 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[5]
- The final results of this study are presented elsewhere at this conference (Poster #P2.01-99)[6]
- 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; PFS, progression-free survival; SAE, serious adverse event; TKI, tyrosine kinase inhibitor; TTSP, time to symptomatic progression

Objectives

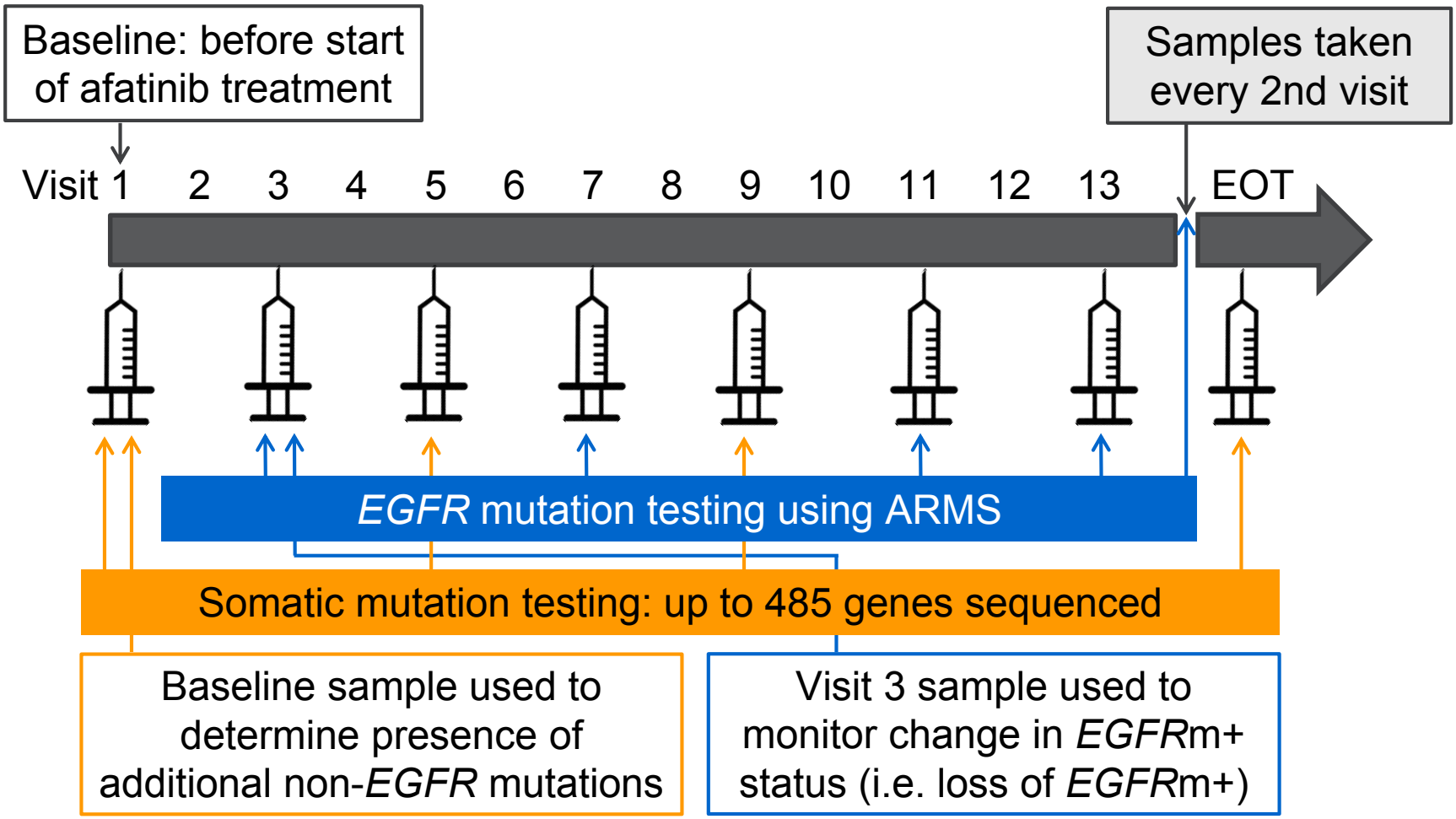
- The aim of this biomarker sub-study was to explore the relationship between tumour mutation type and patients' response to afatinib in terms of efficacy and tolerability

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[5]
- 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 the presence of additional, non-*EGFR* mutations at baseline, and change in mutation status at Visit 3 (see Figure)

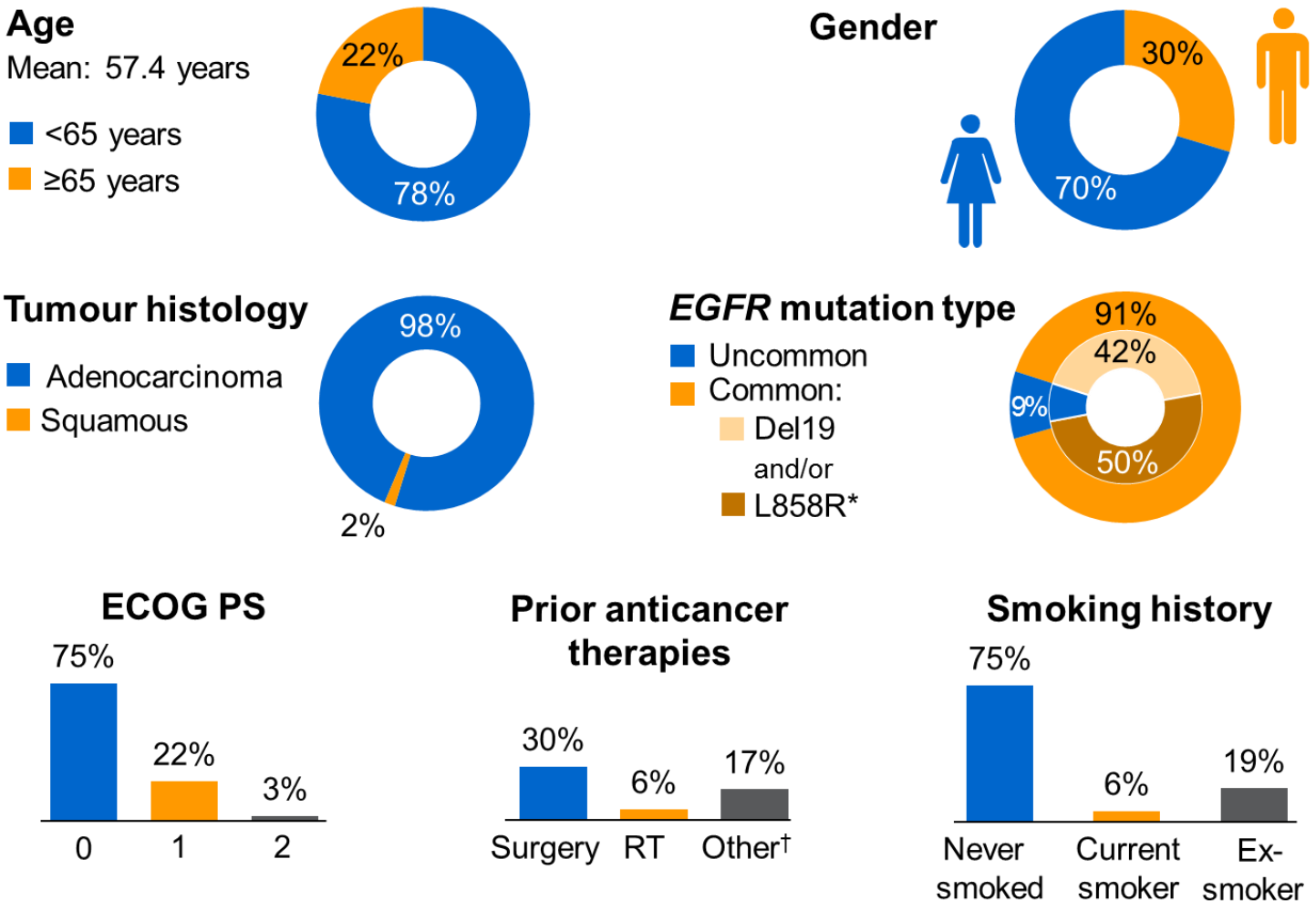
ECOG PS, Eastern Cooperative Oncology Group Performance Status

Methods – biomarker analyses



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

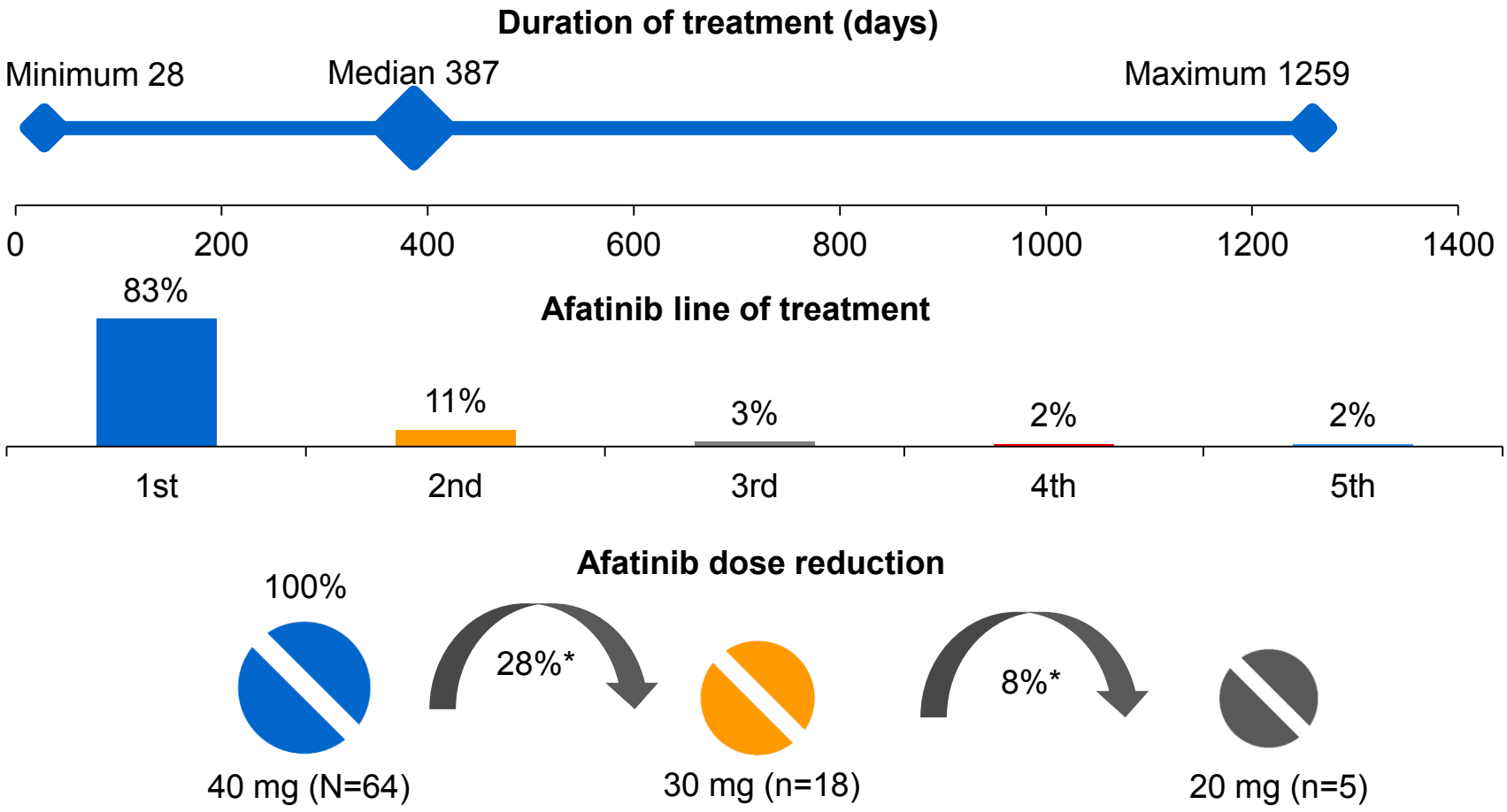
Baseline characteristics (N=64)



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; RT, radiotherapy

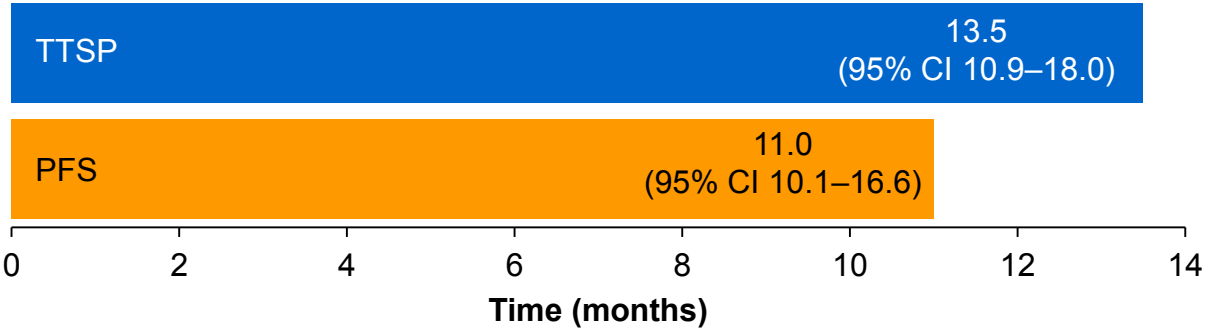
Treatment exposure



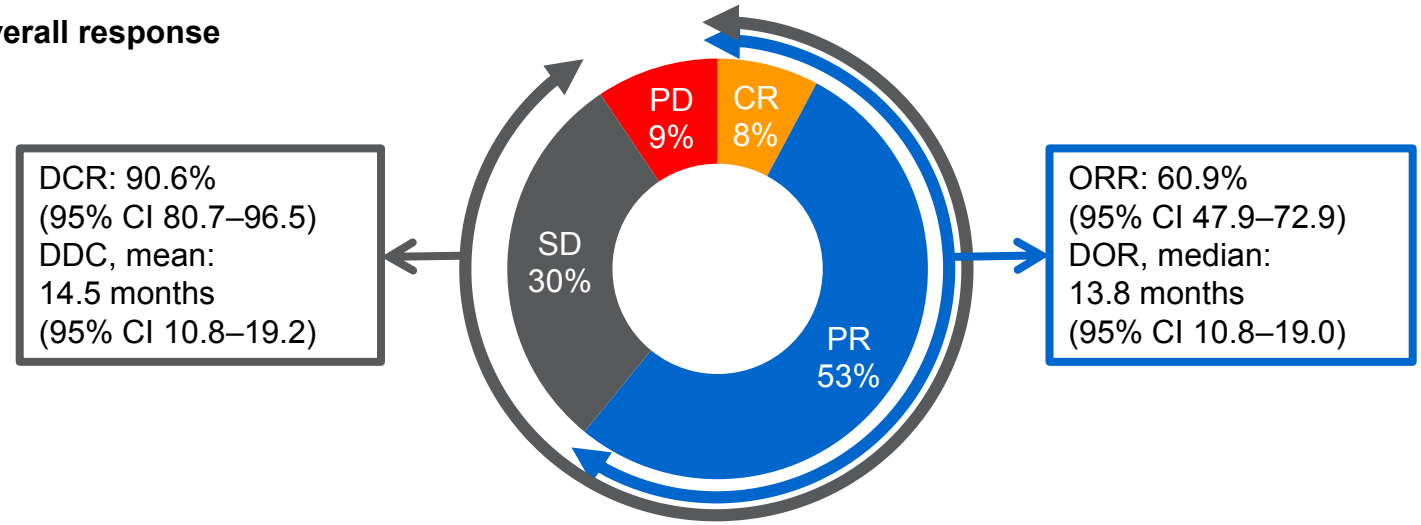
*Percentage of total population (N=64)

Overall efficacy in biomarker analysis patients (N=64)

Overall median TTSP and PFS

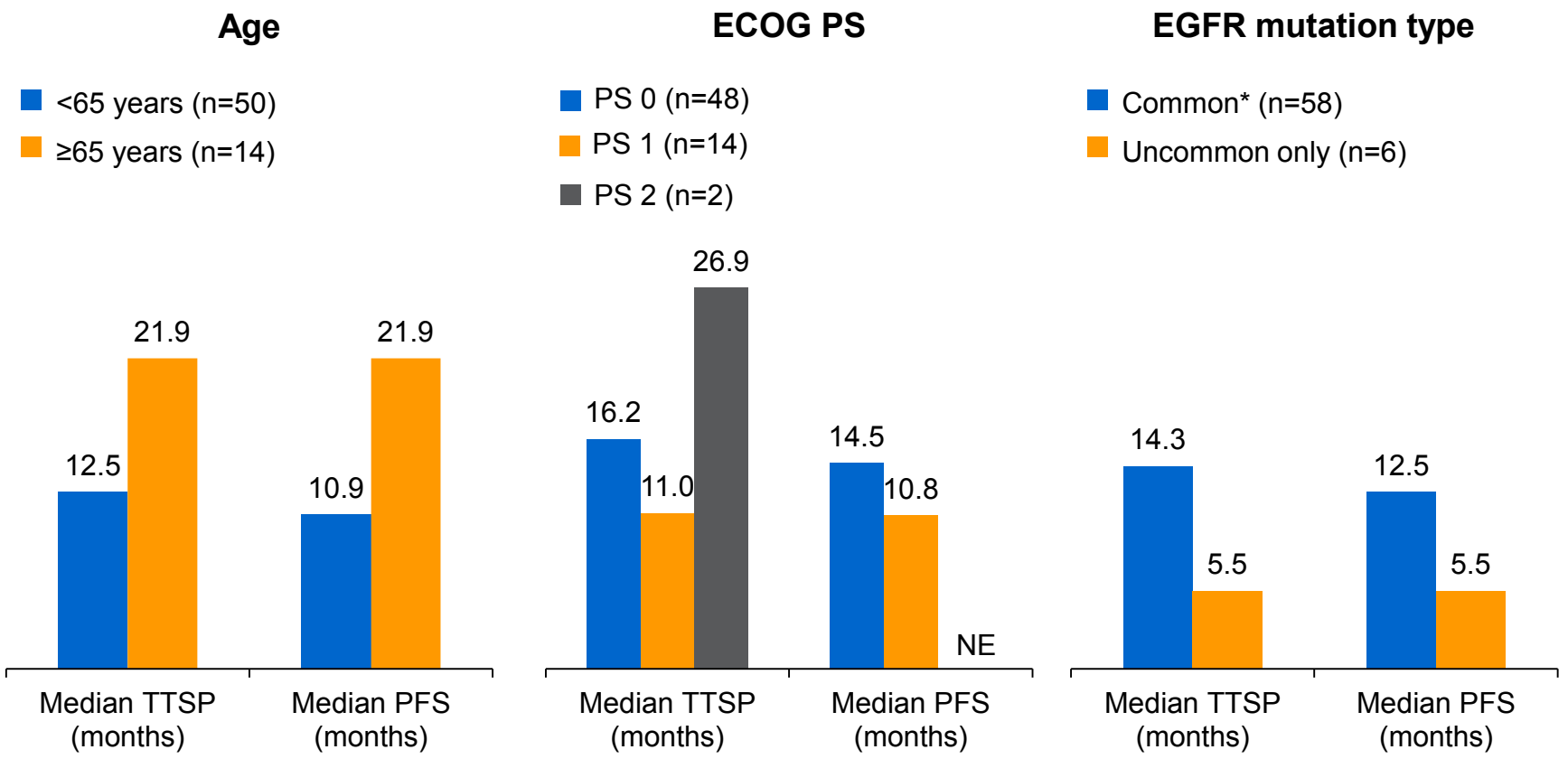


Best overall response



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

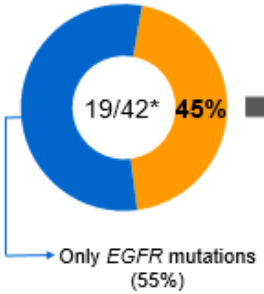
Efficacy by subgroup



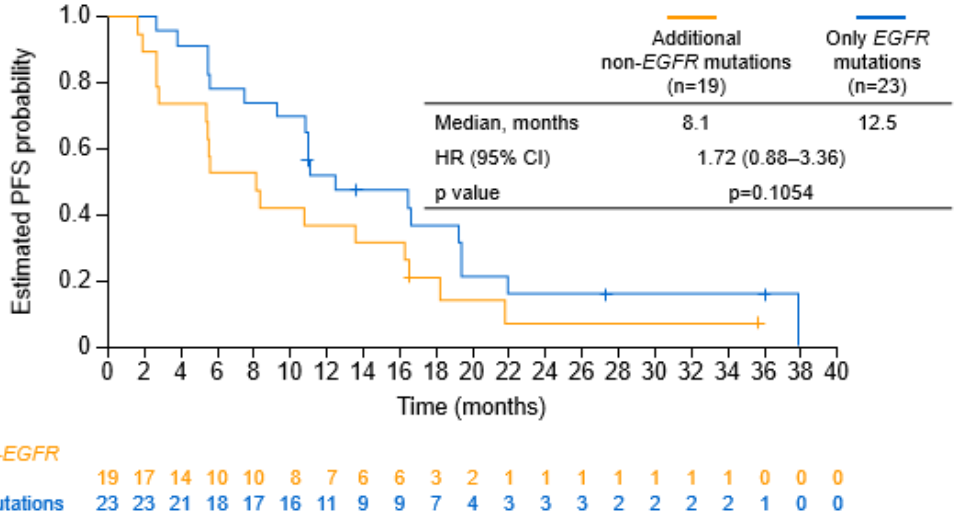
*Del19/L858R; NE, not evaluable

Biomarker analysis

Additional non-*EGFR* mutations at baseline



- Mutations included: *TP53*, *RB1*, *MET*, *ErbB2*, *KRAS*, *BRAF*, *RET*, *ROS1*, *PTEN*, *PIK3CA*
- 17/19 (90%) progressed or died

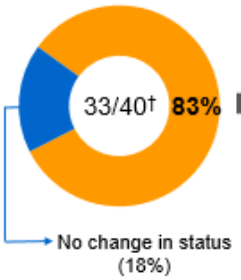


Percentages may not total 100% due to rounding

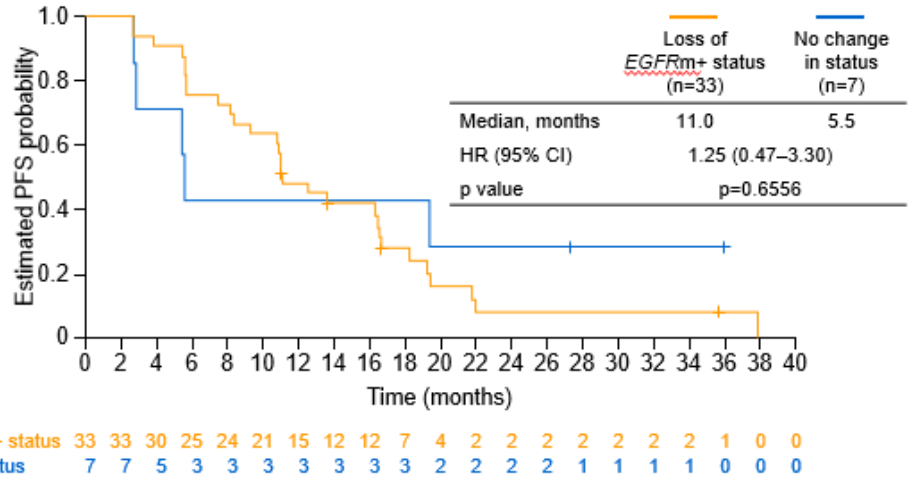
*42 patients were tested for presence of non-EGFR mutations

Biomarker analysis (cont'd)

Loss of EGFRm+ status at Visit 3



29/33 (88%) progressed or died



Percentages may not total 100% due to rounding
†40 patients had available test results of EGFR mutation status

Safety (N=64)

	Afatinib 40 mg/day			
n (%)	**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)†	-	-	-
DRAEs in ≥20% of patients				
Total with DRAE	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), and 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, and CNS metastases (both n=2, 3%). The remaining SAEs occurred in single patients only; ‡Grouped terms

ALT, alanine aminotransferase; CNS, central nervous system; DRAE, drug-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 #P2.01-99)[4] and pivotal randomised controlled trials of afatinib[1,2]
  - In this sub-study, clinical benefit was also demonstrated across all subgroups assessed

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