Second-line afatinib for patients with locally advanced or metastatic NSCLC harbouring common EGFR mutations: a Phase IV study

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Introduction

- The oral, irreversible ErbB family blocker afatinib is approved in many countries for the treatment of *EGFR* mutation-positive (*EGFR*m+) locally advanced or metastatic NSCLC
  - The recommended starting dose of afatinib is 40 mg/day
- Afatinib improved PFS versus chemotherapy in the LUX-Lung 3 and 6 trials,[1,2] and versus gefitinib in LUX-Lung 7[3] in patients with *EGFR*m+ NSCLC receiving first-line afatinib 40 mg/day
- The LUX-Lung 2 study[4] supports the use of second-line afatinib in patients with *EGFR*m+ NSCLC progressing following first-line platinum-based chemotherapy, but only 7/68 (10%) patients received afatinib 40 mg/day; most patients (90%) received afatinib 50 mg/day
  - As such, data supporting the use of afatinib 40 mg/day as second-line therapy in patients with *EGFR*m+ NSCLC are limited

PFS, progression-free survival

Objectives

- The aim of this trial was to assess the efficacy and safety of afatinib 40 mg/day as second-line therapy in patients with advanced/metastatic NSCLC harbouring EGFR common mutations (Del19 and/or L858R), who had progressed following first-line platinum-based chemotherapy and were EGFR TKI-naïve

Methods

- Multicenter, open-label, single-arm Phase IV study conducted across 24 sites in 7 countries (Egypt, Malaysia, Philippines, Poland, Romania, Serbia, and Thailand)

Key inclusion criteria

- Aged ≥18 years
- Del19 and/or L858R
- ECOG PS 0 or 1
- Confirmed stage IIIB or IV lung adenocarcinoma
- Radiologically confirmed progression or recurrence following first-line chemotherapy

Key exclusion criteria

Previous treatment with:

- More than 1 prior line of therapy*
- Less than 3 cycles of platinum-based chemotherapy
- Any EGFR-targeting TKI or antibody
- Any treatment within 3 weeks prior to the start of trial
- Major surgery within 4 weeks before starting trial

*Not counting radiotherapy, radiosensitisers, and/or intrapleural administration of anti-cancer agents.

ECOG PS, Eastern Cooperative Oncology Group performance status

Method (cont'd)

- Eligible patients received afatinib 40 mg/day
- If patients developed grade ≥3 drug-related adverse events (AEs), grade 2 diarrhoea for more than 2 days, or rash for more than 7 days, treatment was interrupted until recovery to grade ≤1, followed by dose reduction in 10 mg decrements
- Patients were treated with afatinib until disease progression or discontinuation for other reasons

Methods (cont'd)

Endpoints

Primary	• OR* (RECIST v1.1)
Secondary	• Disease control† • PFS
Safety	• Intensity and incidence of AEs‡

- Efficacy and safety were evaluated in a descriptive manner, and there were no formal statistical hypotheses

*Defined as CR or PR;
†Defined as CR, PR, or SD;
‡Graded according to US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0

AE, adverse event; CR, complete response; OR, objective response; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

Results

Patients and treatment

- 60 patients received at least one dose of afatinib 40 mg/day (Table 1)
- 86.7% of patients were treated for at least 90 days; mean treatment duration was 336.7 days

Table 1. Patient disposition

	Afatinib 40 mg/day	
	n	%
Enrolled	70	
Treated	60	
Patients discontinued from afatinib	60	100.0
Progressive disease according to RECIST	24	40.0
Clinical signs and symptoms of progression	2	3.3
AEs	12	20.0
Non-compliant with protocol	1	1.7
Lost to follow-up	0	0.0
Refused to continue afatinib	1	1.7
Other*	20	33.3

*Switched to commercially-available afatinib

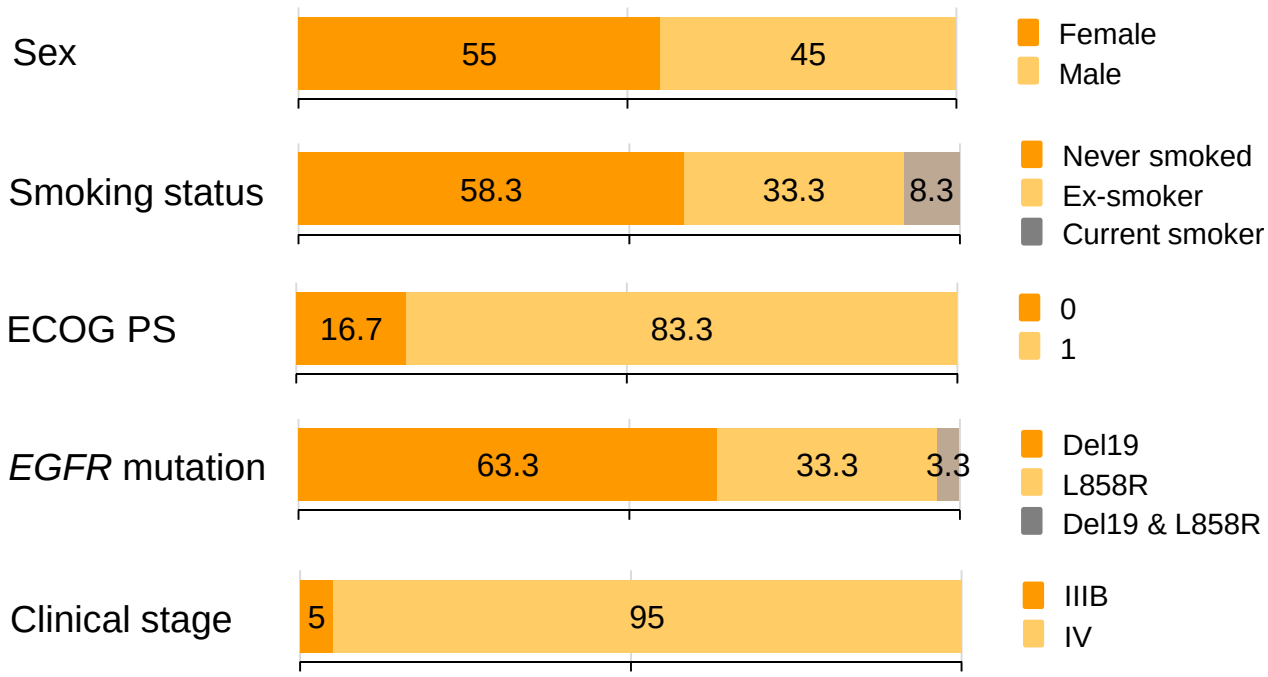
Results (cont’d)

Patient demographics and baseline characteristics

- Patients were mostly white (68.3%) and had a mean age (Std dev) of 59.9 (9.8) years
- The most frequent sites of distant metastases were the ipsilateral lung (48.3%) and contralateral lung (45.0%), while 15.0% of patients had brain metastases at screening
- All patients had prior chemotherapy, while 17 (28.3%) and 18 (30.0%) had surgery and radiotherapy, respectively

Std dev, standard deviation

Results (cont'd)



Efficacy

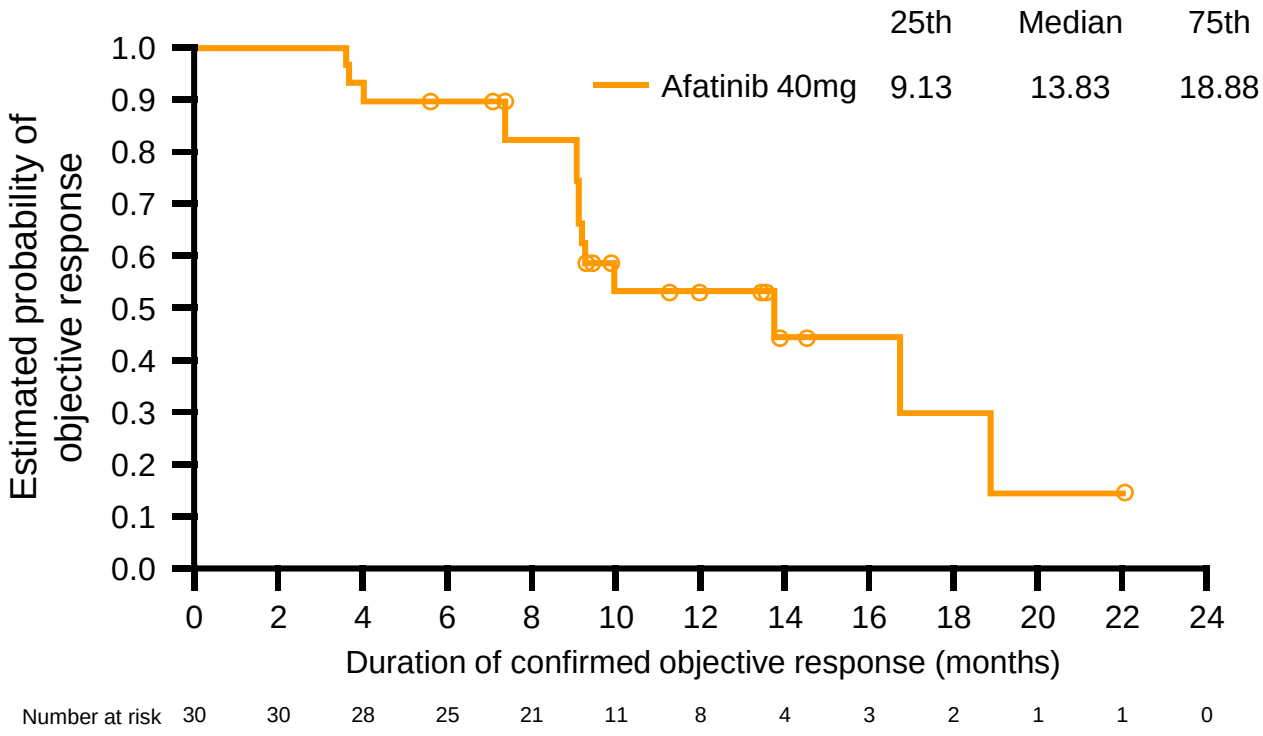
Objective response

- The primary study endpoint of OR by investigator assessment was achieved by 30 (50%) patients
- 29 (48.3%) patients achieved PR, one (1.7%) patient had a CR, and 20 (33.3%) had stable disease
- Median duration of response was 13.8 months (95% CI: 9.16, 18.88)

CI, confidence interval

Efficacy (cont'd)

Kaplan–Meier curve of duration of OR



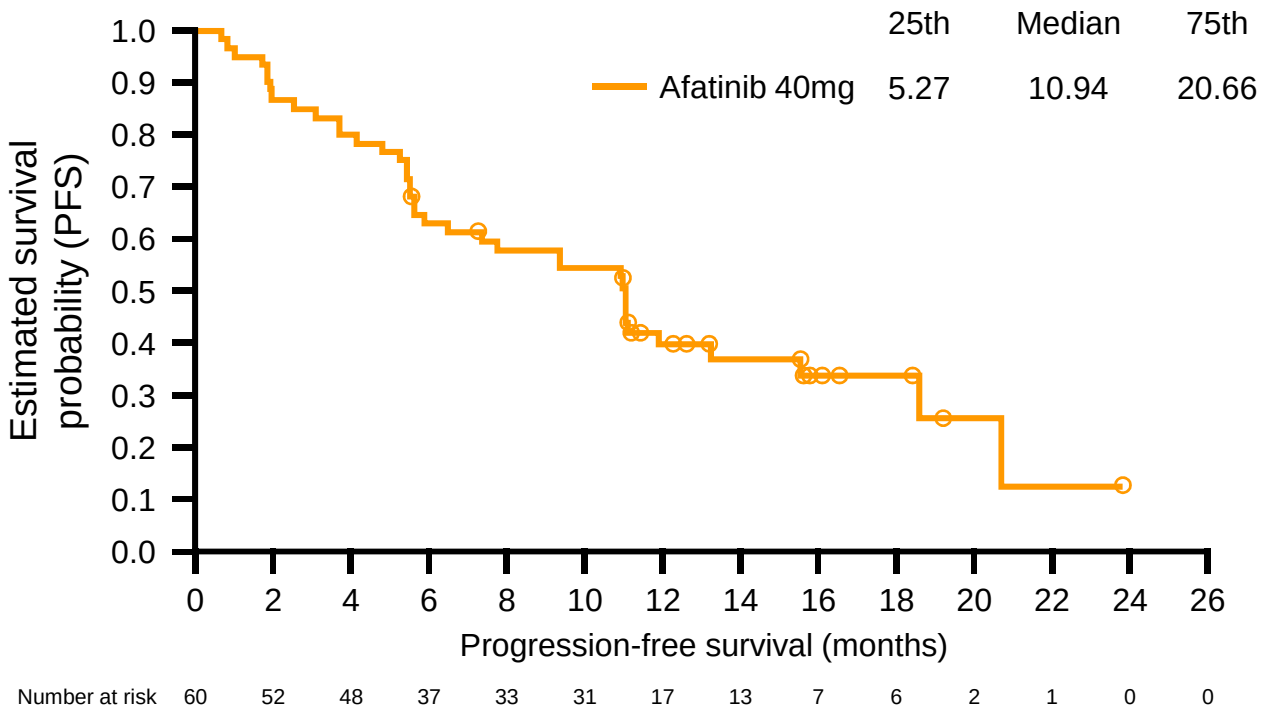
Efficacy (cont’d)

Progression-free survival

- 39 patients (65.0%) experienced an event contributing to PFS analysis (i.e. disease progression as determined by investigator assessment, or death)
- Median PFS was 10.9 months (95% CI: 6.4, 13.2)

Efficacy (cont’d)

Kaplan–Meier curve of PFS



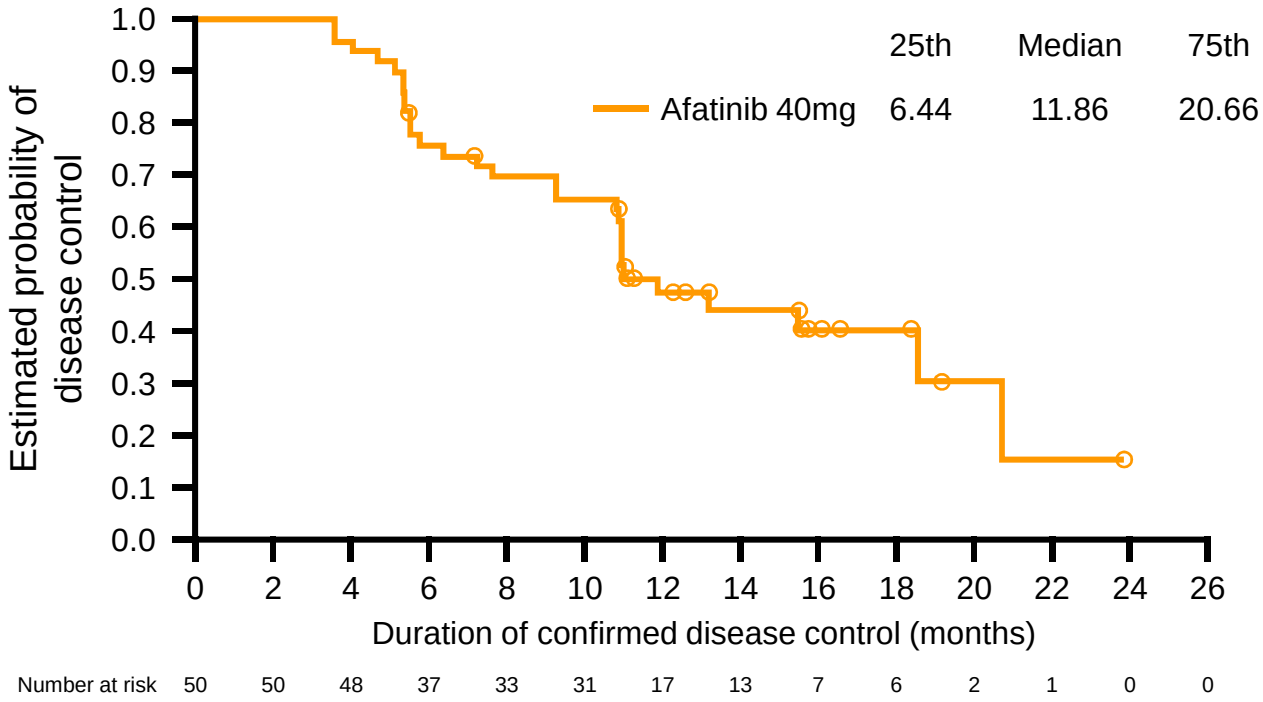
Efficacy (cont’d)

Disease control

- 50 patients (83.3%) showed confirmed disease control
- Median duration of disease control was 11.9 months (95% CI: 10.8, 20.7)

Efficacy (cont’d)

Kaplan–Meier curve of duration of disease control



Safety

- Most patients (91.7%) had at least one AE of any grade deemed to be treatment-related by the investigator
- The most commonly occurring drug-related AEs of any grade were diarrhoea (71.7%), rash (28.3%), paronychia (23.3%), mucosal inflammation (18.3%) and dermatitis acneiform (16.7%)
- 25 patients (41.7%) had dose reduction to 30 mg/day, with six patients (10.0%) having a further dose reduction to 20 mg/day
- 12 patients (20%) experienced AEs that led to permanent discontinuation of afatinib

Safety (Cont'd)

Summary of AEs

	Afatinib 40 mg/day	
Patients	**n**	**%**
Any AE	57	95.0
Afatinib-related AEs	55	91.7
AEs leading to afatinib dose reduction	25	41.7
AEs leading to afatinib discontinuation*	12	20.0
Other significant AEs (according to ICH E3†)	25	41.7
Serious AEs‡	21	35.0
AEs by highest CTCAE grade		
Grade 1 or 2	32	53.3
Grade ≥3	25	41.7

*16 patients had AEs leading to discontinuation, but the reason for discontinuation in 4 patients was reported as PD according to RECIST or as clinical signs and symptoms of progression;
†Guideline from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) on the structure and content of clinical study reports;
‡Patients could be counted in more than one category of serious AE.

Summary

- 50% of patients achieved a confirmed OR, with a median duration greater than 1 year; median PFS was 10.9 months
- More than 80% of patients had disease control, with a median duration of 11.9 months
- The safety and tolerability profile of afatinib was consistent with the known safety profile of afatinib, with the most common afatinib-related AEs observed being diarrhoea and rash
- The current study supports the use of afatinib as second-line therapy at the recommended 40 mg/day starting dose in EGFR TKI-naïve patients with locally advanced/metastatic NSCLC harbouring common *EGFR* mutations (Del19 or L858R), after failure of first-line chemotherapy

References

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