National Translational Medicine and
Clinical Trial Resource Center
國家轉譯醫學與臨床試驗資源中心

Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial

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Introduction

- Afatinib is a novel small-molecule ErbB-family blocker. It covalently binds and irreversibly blocks signalling from all homodimers and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4.
- preclinical activity against cancer cells harbouring activating EGFR mutations, including the common mutations (exon 19 deletion and L858R)
- prevented tumour growth progression and in some cases even caused tumour regression

Introduction

- Phase 1 studies of afatinib were done in patients with solid tumours
  - the maximum tolerated dose was 50 mg once a day
  - diarrhoea and rash

Aim

- The authors aimed to assess the efficacy of afatinib in patients with lung adenocarcinoma and EGFR mutations.

Method

- Study design and patients
- Procedures
- Statistical analysis
- Role of the funding source

Study design

- LUX-Lung 2 was a **single-arm**, **phase 2 study** to explore the anti-tumour efficacy of afatinib in patients with lung adenocarcinoma.

Patient inclusion criteria

- stage IIIB (with pleural effusion) or stage IV disease with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2
- asymptomatic brain metastasis were eligible if they had stable brain disease for at least 4 weeks without having needed steroids or antiepileptics
- only patients who have progressed or relapsed after one previous chemotherapy regimen

Patient exclusion criteria

- Treatment
  - received any chemotherapy, hormone therapy, or immunotherapy in the previous 4 weeks, or had radiotherapy in the 2 weeks before the trial treatment began
  - previously treated with EGFR-inhibiting agents
- Syndrome
  - with serious gastrointestinal disorders with diarrhoea as a major symptom; serious active infection
  - heart disease or dysfunction
  - abnormal liver, renal, or haematological function
  - other malignancies within the past 5 years

Procedures

- Does and treatment cycles
  - Patients were treated with afatinib 50 mg once a day. After a protocol amendment, patients were treated with afatinib 40 mg once a day.
  - Treatment cycles (4 weeks in length) continued until disease progression, intolerable adverse events, or if patients withdrew.

Procedures

- Tumour assessment
  - was done by CT scan or MRI of patients' chest to pelvis, at baseline, week 4, week 8, and week 12, and at 8 week intervals thereafter
  - RECIST 1.0 to establish treatment response. Imaging scans were also sent for central review, where two radiologists independently established response to treatment.

Procedures

- Safety assessments
  - blood counts
  - biochemical analysis of serum samples.
  - left ventricular ejection fraction by echocardiogram or radionucleotide scan every three cycles to monitor for possible cardiac toxicity.

Procedures

- Adverse events
  - by National Cancer Institute Common Terminology Criteria version 3.0.
  - grade 3 or higher drug-related adverse events
  - if patients again encountered adverse events requiring a pause in treatment, they further reduced their dose by 10 mg after resolution of adverse events.
  - after a third occurrence, afatinib was discontinued.

Statistical analysis

- Primary endpoint
  - the proportion of patients with a confirmed objective response
    - Complete response or partial response
    - Confirmed by a second scan at least 4 weeks after the first), as determined by RECIST 1.0.

Statistical analysis

- Secondary efficacy endpoints
  - the proportion of patients with disease control (ie, an objective response or stable disease)
    - time to objective response
    - duration of objective response
  - tumour shrinkage
  - progression-free survival(PFS)
  - overall survival(OS)

Statistical analysis

- Exact 95% CI
  - the proportion of patients with an objective response or disease control.
- Kaplan-Meier estimates with 95% CI using

  Greenwood's SE estimate
  - median progression-free survival
  - overall survival
  - duration of response

Statistical analysis

- The authors estimated that the trial would provide sufficient precision to estimate the 95% CI for the proportion of patients with an objective response with a width of 22.6% in the overall population, assuming that the underlying ORR was 55%.

Results-figure 1

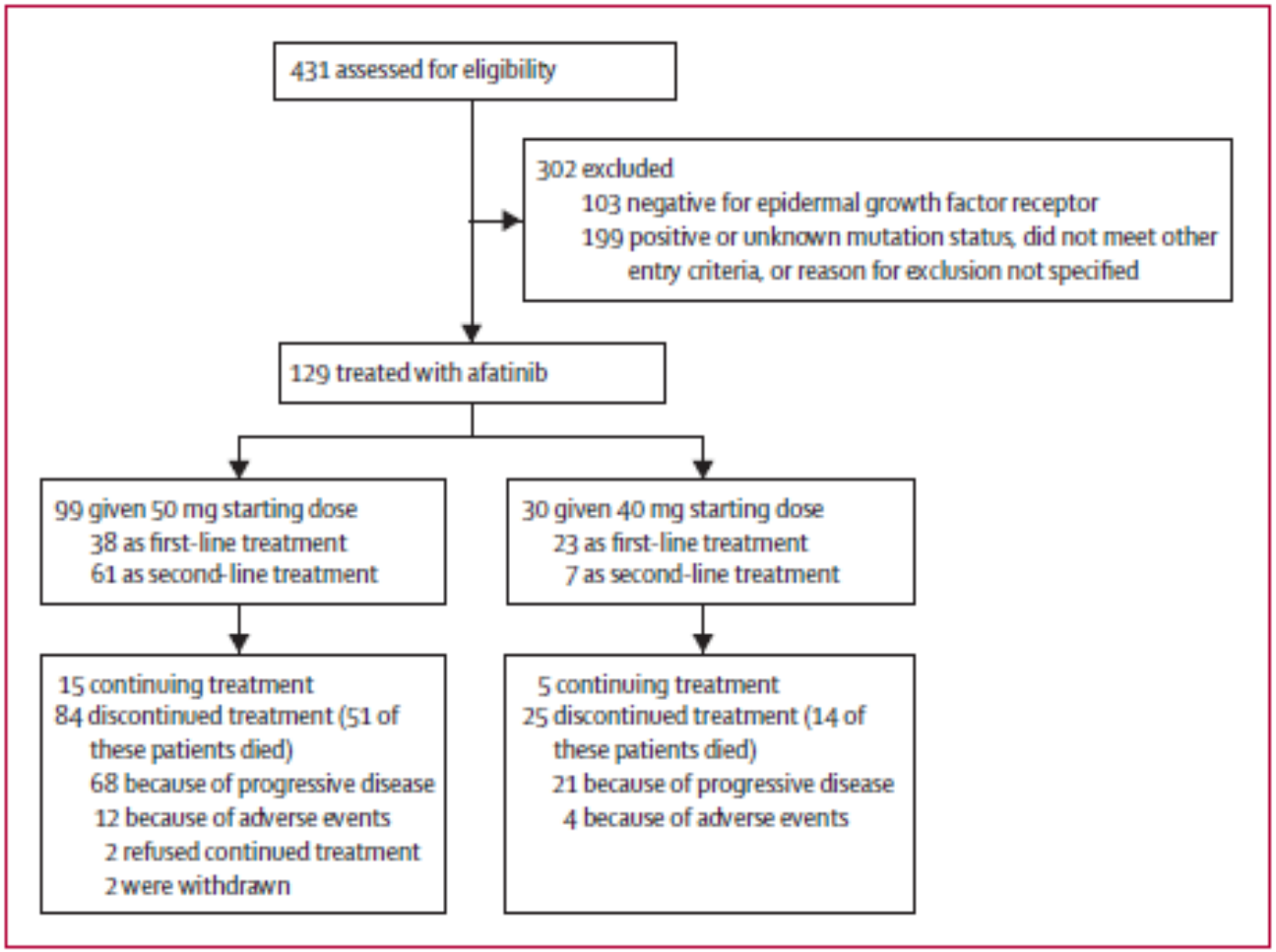


Figure 1: Trial profile

Results

	First-line treatment (n=61)	Second-line treatment (n=68)	Total (n=129)
Median age (years [range])	62 (46–86)	61 (35–82)	61 (35–86)
Sex			
Male	21 (34%)	33 (49%)	54 (42%)
Female	40 (66%)	35 (51%)	75 (58%)
Ethnic origin			
Asian	48 (79%)	64 (94%)	112 (87%)
White	12 (20%)	4 (6%)	16 (12%)
Black	1 (2%)	0	1 (1%)
ECOG performance status			
0	44 (72%)	39 (57%)	83 (64%)
1	16 (26%)	26 (38%)	42 (33%)
2	1 (2%)	3 (4%)	4 (3%)
Smoking history			
Never-smoker	41 (67%)	41 (60%)	82 (64%)
Ex-smoker with <15 pack years	4 (7%)	8 (12%)	12 (9%)
Current or other ex-smoker	16 (26%)	19 (28%)	35 (27%)
EGFR mutation type			
Del19	29 (48%)	23 (34%)	52 (40%)
L858R	22 (36%)	32 (47%)	54 (42%)
Other	10 (16%)	13 (19%)	23 (18%)
Clinical stage (at screening)			
IIIB	5 (8%)	3 (4%)	8 (6%)
IV	56 (92%)	65 (96%)	121 (94%)
Starting dose of afatinib			
40 mg	23 (38%)	7 (10%)	30 (23%)
50 mg	38 (62%)	61 (90%)	99 (77%)

ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

Results-table 2

objective response | Disease control

	All patients (n=129)		Del19 or L858R (n=106)		Other mutations (n=23)	
	Independent review	Investigator assessment	Independent review	Investigator assessment	Independent review	Investigator assessment
Complete response	2 (2%)	0	2 (2%)	0	0	0
Partial response	77 (60%)	78 (60%)	68 (64%)	68 (64%)	9 (39%)	10 (43%)
Stable disease	27 (21%)	33 (26%)	23 (22%)	25 (24%)	4 (17%)	8 (35%)
Progressive disease	18 (14%)	9 (7%)	9 (8%)	6 (6%)	9 (39%)	3 (13%)
Not assessable	5 (4%)	9 (7%)	4 (4%)	7 (7%)	1 (4%)	2 (9%)

Table 2: Best confirmed treatment response according to RECIST 1.0

Results-figure 2

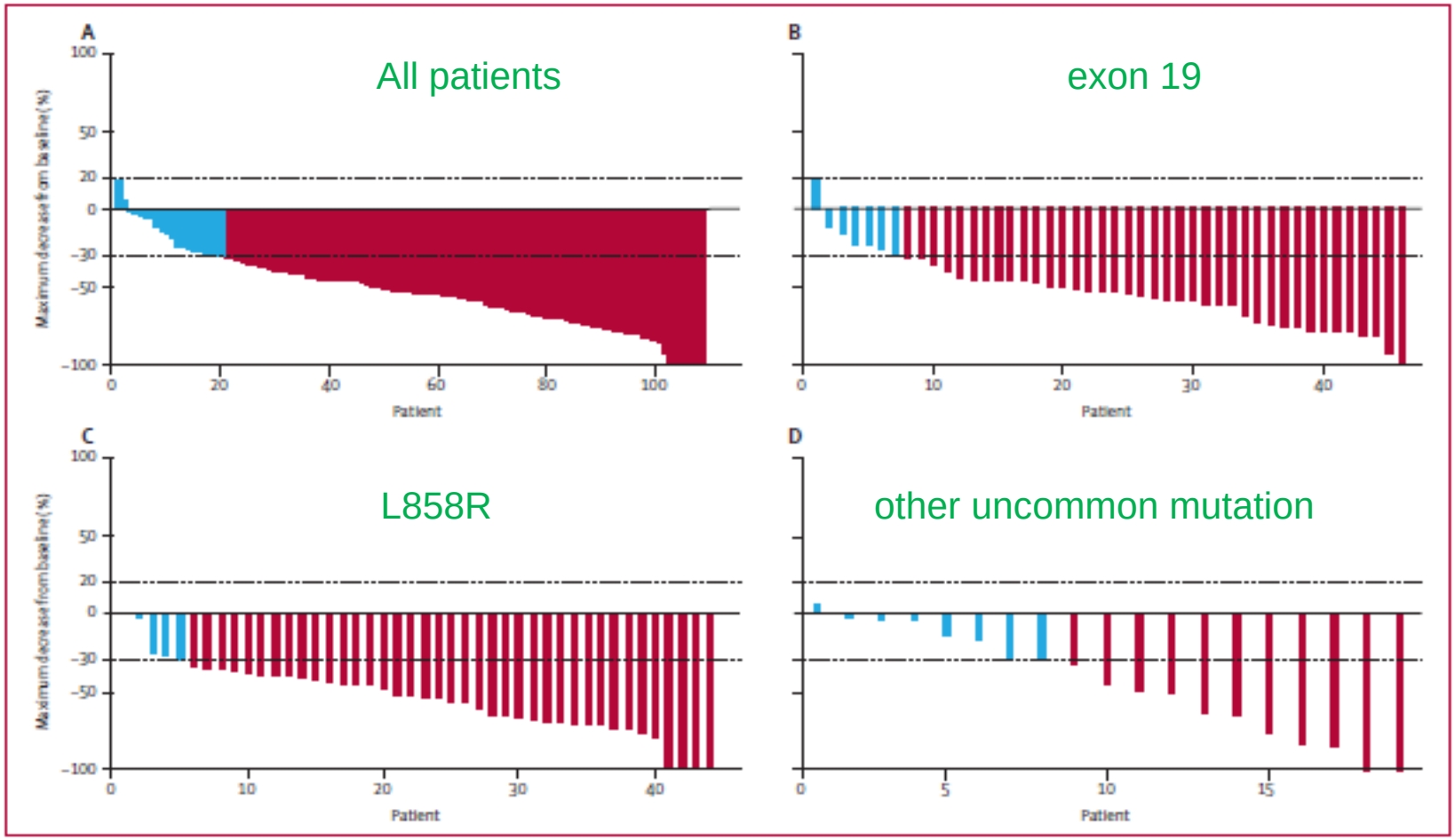
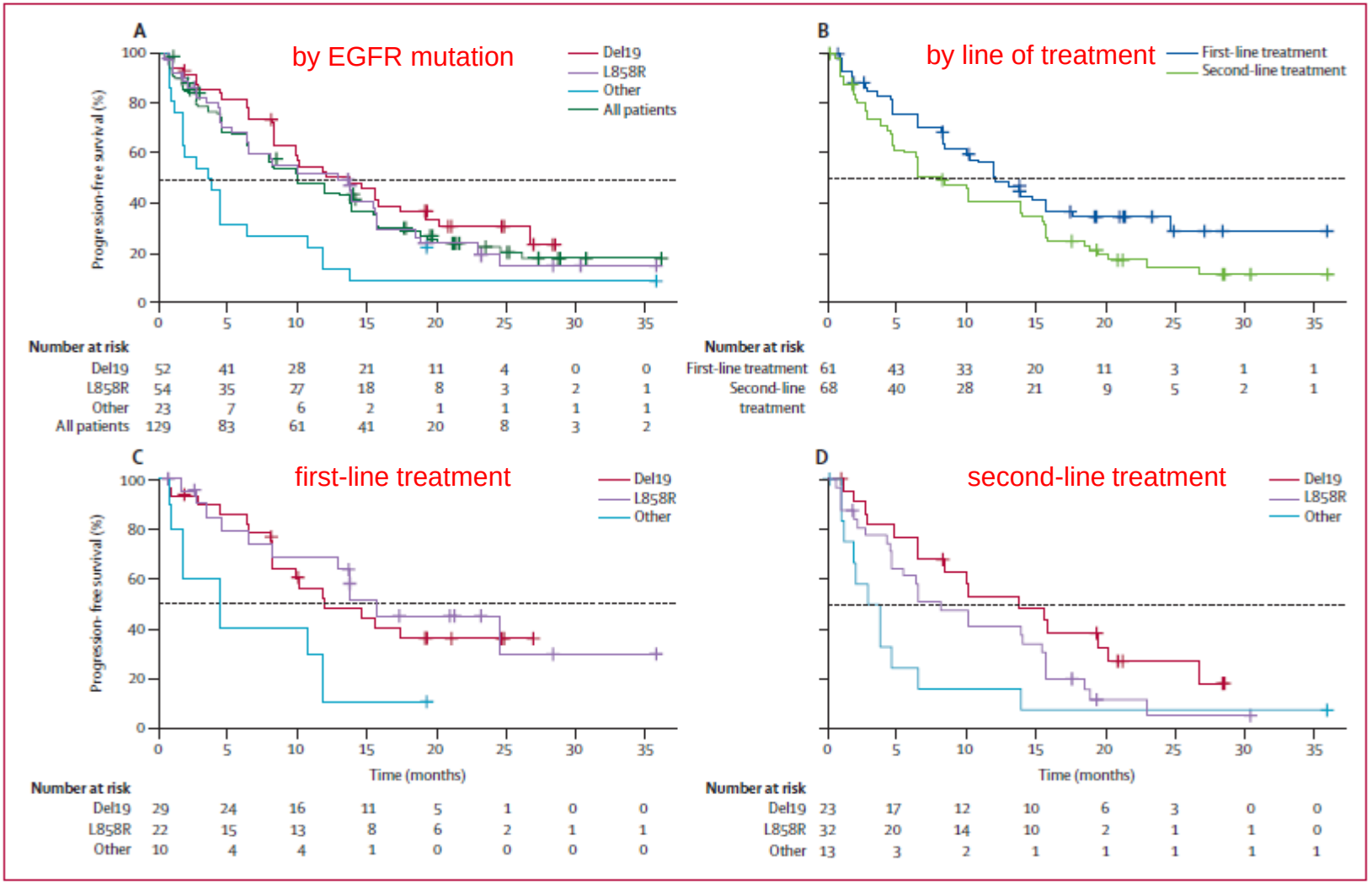


Figure 2: **Waterfall plots of percent change from baseline in measurable tumour at the time of best response (by independent review)**
All patients (A); patients with EGFR exon 19 deletion (B); patients with EGFR exon 21 L858R mutation (C), and patients with other uncommon EGFR mutations (D). Data for patients with a decrease from baseline of 30% or more are given in red; data for patients with an increase from baseline of less than 20% to a decrease from baseline of less than 30% are given in blue. These plots include patients with target lesions measured at baseline and at least one post-baseline visit. Data are therefore not available for patients who did not have target lesion or post-baseline measurements.

Results-figure 3(PFS)



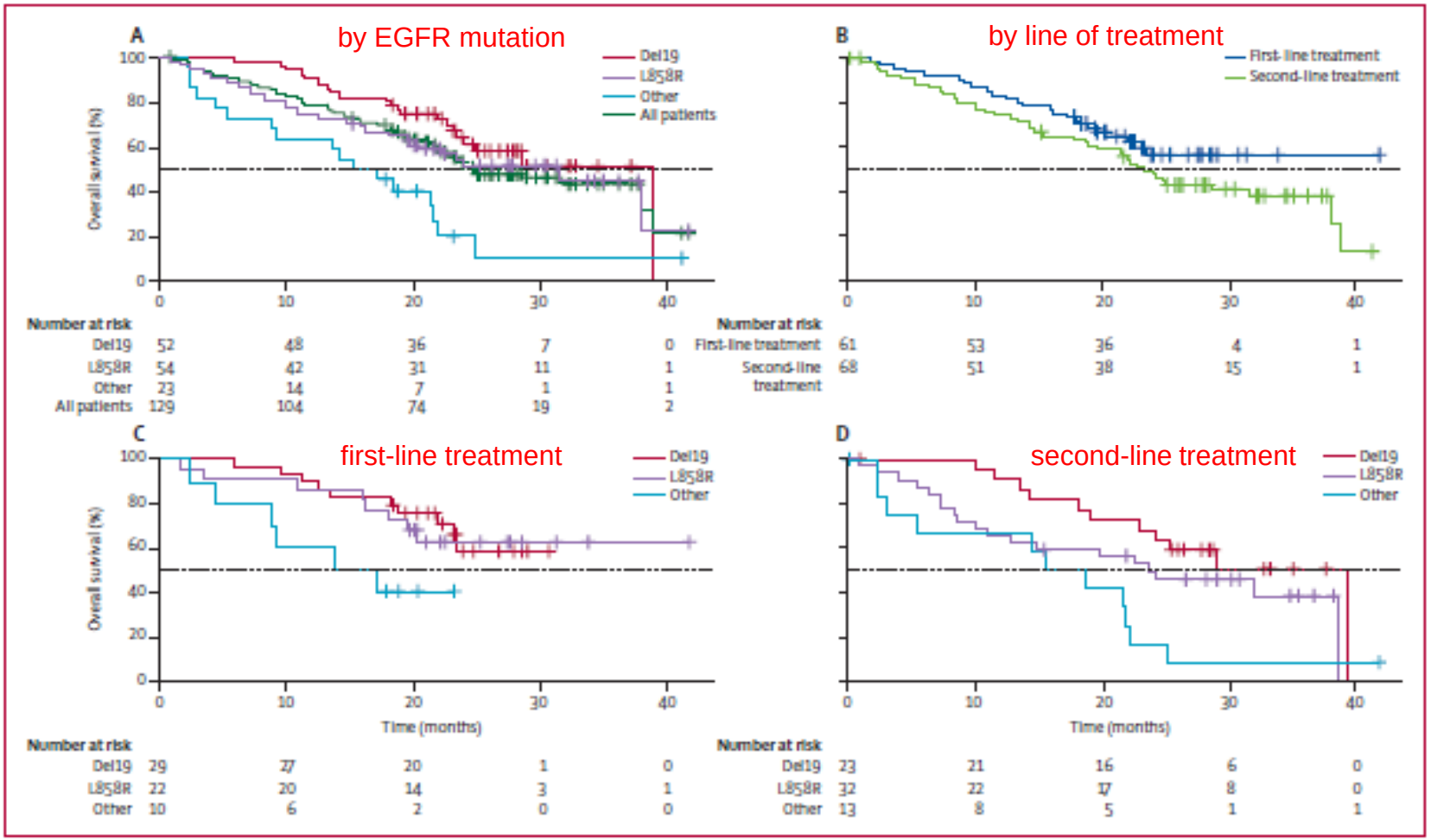
Results-table 3

	Progression-free survival (independent review)		Progression-free survival (investigator assessment)		Overall survival	
	Number of events	Median progression-free survival (months [95% CI])	Number of events	Median progression-free survival (months [95% CI])	Number of events	Median overall survival (months [95% CI])
Irrespective of treatment line						
All patients (n=129)	91	10·1 (8·12–13·80)	96	13·7 (10·91–16·13)	65	24·8 (21·98–38·74)
Del19 (n=52)	33	13·7 (8·31–19·35)	35	15·5 (11·89–22·97)	21	38·7 (23·43–38·74)
L858R (n=54)	38	13·7 (6·37–15·57)	40	15·8 (8·21–20·53)	27	31·5 (19·45–NA)
Other (n=23)	20	3·7 (1·74–6·37)	21	4·6 (2·76–11·83)	17	16·3 (5·36–21·55)
First-line treatment						
All patients (n=61)	37	12·0 (8·21–15·64)	42	15·6 (11·89–20·24)	24	NA (22·01–NA)
Del19 (n=29)	17	12·0 (8·21–NA)	18	15·6 (11·89–22·97–NA)	10	NA (22·01–NA)
L858R (n=22)	11	15·6 (6·44–NA)	14	16·0 (10·91–30·16)	8	NA (17·97–NA)
Other (n=10)	9	4·5 (0·82–11·89)	10	6·0 (0·82–13·73)	6	15·5 (2·37–NA)
Second-line treatment						
All patients (n=68)	54	8·0 (4·63–13·83)	54	10·5 (6·41–17·41)	41	23·3 (18·53–38·01)
Del19 (n=23)	16	13·7 (6·41–20·11)	17	14·6 (8·28–26·71)	11	38·7 (18·92–38·74)
L858R (n=32)	27	8·0 (4·50–15·41)	26	10·1 (6·34–20·53)	19	23·3 (9·99–38·01)
Other (n=13)	11	3·2 (0·89–6·37)	11	4·6 (1·91–13·73)	11	16·9 (2·37–21·98)

NA=not available.

Table 3: Summary of progression-free survival and overall survival by mutation type and line of treatment

Results-figure 4(OS)



Results-table 4

	Afatinib 50 mg (n=99)					Afatinib 40 mg (n=30)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Diarrhoea	35 (35%)	36 (36%)	22 (22%)	0	93 (94%)	19 (63%)	8 (27%)	2 (7%)	0	29 (97%)
Rash or acne*	19 (19%)	46 (46%)	28 (28%)	0	93 (94%)	13 (43%)	12 (40%)	2 (7%)	0	27 (90%)
Stomatitis*	43 (43%)	38 (38%)	8 (8%)	0	89 (90%)	10 (33%)	5 (17%)	0	0	15 (50%)
Nail effect*†	31 (31%)	46 (46%)	8 (8%)	0	85 (86%)	8 (27%)	14 (47%)	2 (7%)	0	24 (80%)
Pruritus	32 (32%)	26 (26%)	1 (1%)	0	59 (60%)	11 (37%)	3 (10%)	0	0	14 (47%)
Dry skin	27 (27%)	6 (6%)	0	0	33 (33%)	6 (20%)	1 (3%)	0	0	7 (23%)
Rhinorrhoea	29 (29%)	2 (2%)	0	0	31 (31%)	7 (23%)	1 (3%)	0	0	8 (27%)
Decreased appetite	15 (15%)	11 (11%)	1 (1%)	0	27 (27%)	4 (13%)	4 (13%)	1 (3%)	0	9 (30%)
Epistaxis	24 (24%)	1 (1%)	0	0	25 (25%)	9 (30%)	0	0	0	9 (30%)
Ocular effect*‡	19 (19%)	9 (9%)	0	0	28 (28%)	6 (20%)	0	0	0	6 (20%)
Fatigue*	12 (12%)	9 (9%)	2 (2%)	0	23 (23%)	5 (17%)	2 (7%)	1 (3%)	0	8 (27%)
Nausea	7 (7%)	4 (4%)	1 (1%)	0	12 (12%)	4 (13%)	1 (3%)	0	0	5 (17%)
Vomiting	5 (5%)	2 (2%)	2 (2%)	0	9 (9%)	4 (13%)	0	1 (3%)	0	5 (17%)
Weight loss	9 (9%)	6 (6%)	0	0	15 (15%)	2 (7%)	1 (3%)	0	0	3 (10%)
Lip effect*§	12 (12%)	2 (2%)	0	0	14 (14%)	2 (7%)	0	0	0	2 (7%)
Muscle spasm	7 (7%)	3 (3%)	0	0	10 (10%)	1 (3%)	0	0	0	1 (3%)
Xerosis	0	1 (1%)	0	0	1 (1%)	1 (3%)	2 (7%)	0	0	3 (10%)

Data are number (%). Adverse events graded by Common Terminology Criteria for Adverse Events version 3.0. *Group term of closely related adverse events. †The most common events in this category were paronychia and nail disorder. ‡The two most common events in this category were conjunctivitis and dry eye. §Almost all of these were cheilitis.

Table 4: **Treatment-related adverse events recorded in at least 10% of patients by starting dose**

Discussion

- For the less common mutations, the proportion of patients who achieved an objective response was lower than for patients with the more common mutations, but still of clinical importance.

Discussion

- In the combination trial, afatinib plus cetuximab was reported to have greater activity (about 35% of patients had an objective response) than for each drug alone.

Discussion

- Diarrhoea and rash or acne were the most common adverse events in this study; the adverse event profile was similar to that seen with gefitinib or erlotinib.
- Rate of grade 3 or higher adverse events was much lower in patients treated with 40 mg than it was in patients treated with 50 mg.

Discussion

- The author’s findings provided the rationale for two phase 3 trials to compare afatinib at a starting dose of 40 mg with chemotherapy in first-line patients with EGFR mutations.

Thank you for your attention~

Formula

Survival function：

$$\hat{S}_T(t) = \prod_{t_j < t} \left(\frac{n_j - d_j}{n_j}\right)$$

Formula of standard error：

$$S.E.\left\{\hat{S}_T(t)\right\} = \hat{S}_T(t)\sqrt{\sum_{j=1}^{k} \frac{d_j}{n_k(n_j - d_j)}}$$