Supplementary Figure Legends

Supplementary Figure S1. (A) Study design and (B) patient disposition. AE, adverse event; CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Primary efficacy end point – PFS across subgroups

Supplementary Figure S2. Forest plot of progression-free survival. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio.

Supplementary Figure S3. Maximum percentage change from baseline in the size of the target lesions in the (A) afatinib plus paclitaxel arm and (B) investigator's choice of chemotherapy arm.

Supplementary Figure S4. Part A PFS (A) for all patients; (B) according to centrally determined *EGFR* mutation status; (C) according to clinical enrichment criteria; (D) according to tumor histology. EGFR, epidermal growth factor receptor; PFS, progression-free survival.

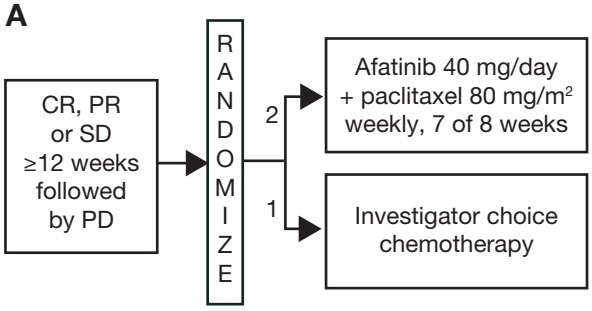
Median PFS during Part A was 3.2 months (supplementary Figure S4A). In patients subsequently randomized, median PFS was 5.6 months. Median PFS was higher in patients with centrally confirmed epidermal growth factor receptor (*EGFR*) mutations

than in patients with wild-type *EGFR* status (supplementary Figure S4B). PFS was also higher in patients who attained higher clinical enrichment criteria (complete response/partial response or ≥48 weeks of benefit on erlotinib/gefitinib) than those who did not (supplementary Figure S4C). PFS was similar in patients with squamous and adenocarcinoma histology (3.7 and 3.2 months, supplementary Figure S4D).

Post-progression therapy in patients who discontinued trial medication

Supplementary Figure S5. Number of lines of subsequent therapy.

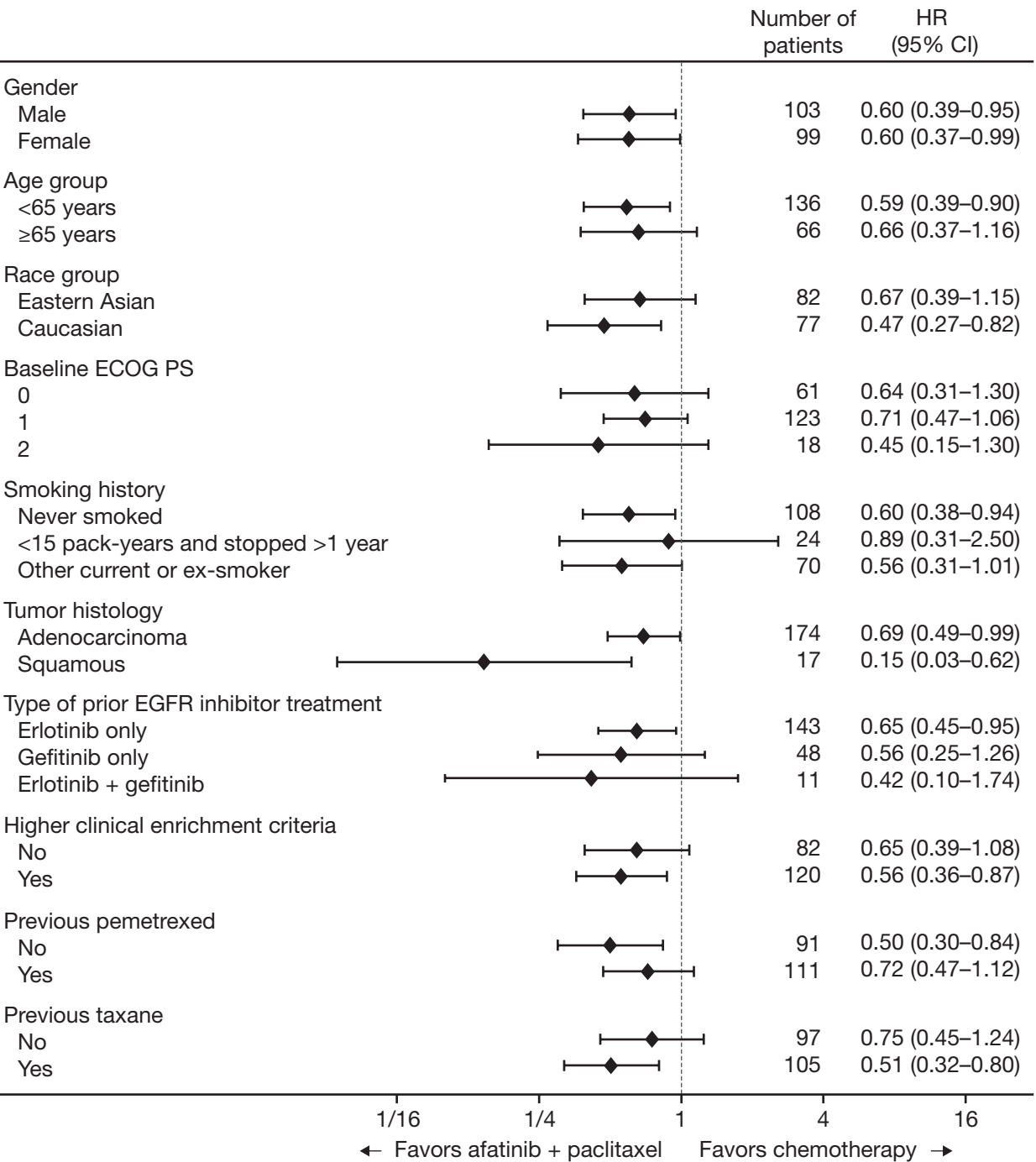
A

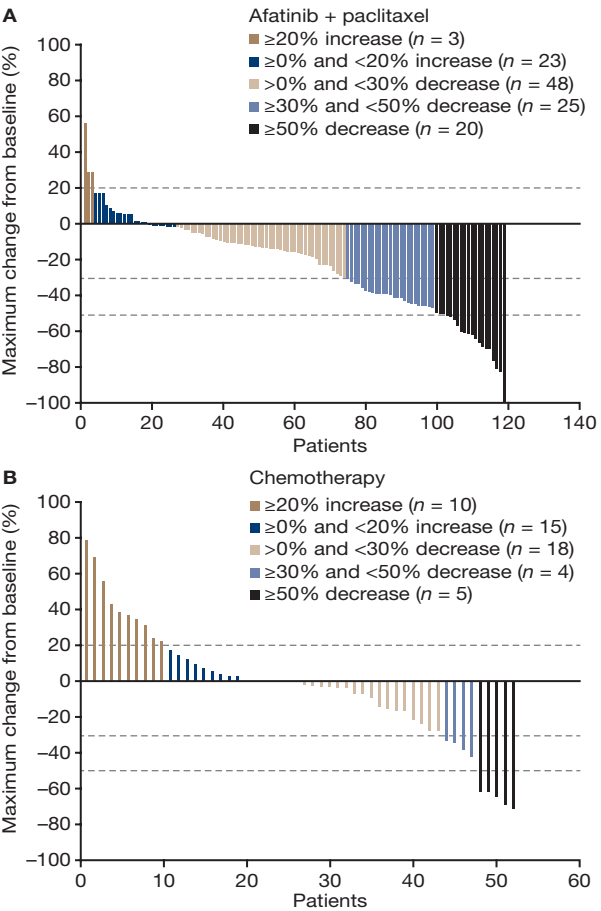


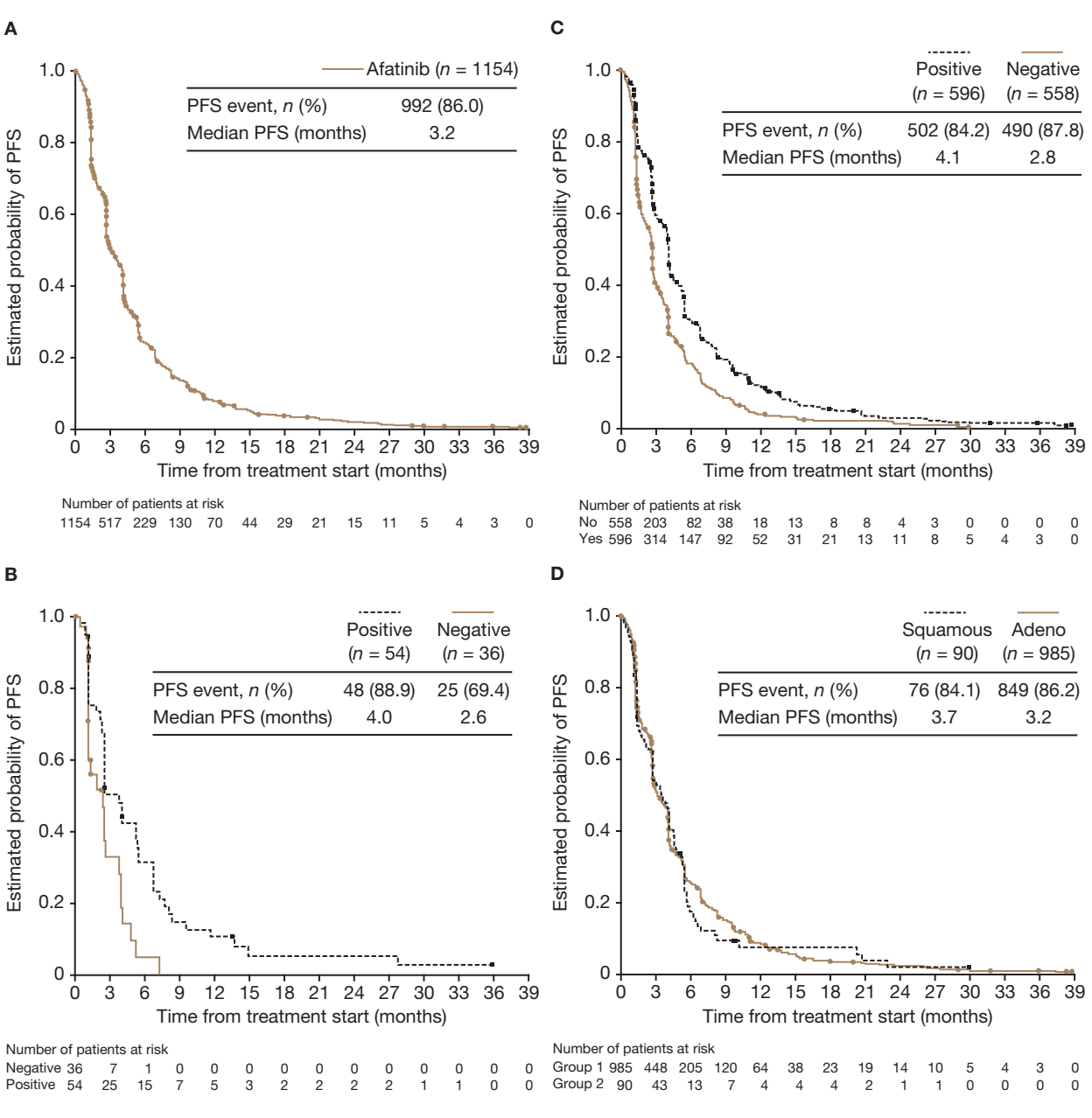
B

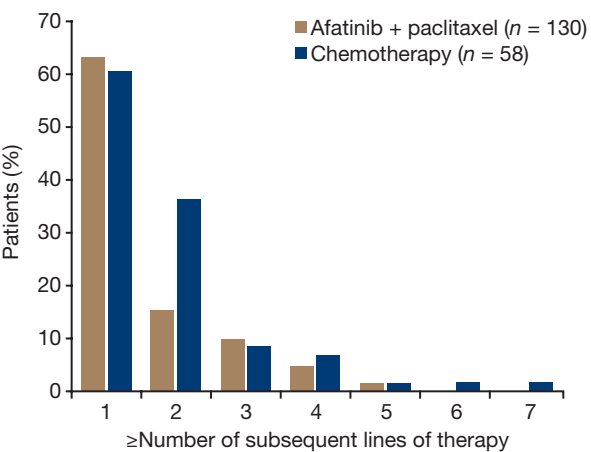
Reasons for discontinuation (%)

	Afatinib + paclitaxel (*n* = 134)	Investigator choice (*n* = 68)
Progressive disease (RECIST)	54.5	65.0
Clinical signs of progression	8.3	1.7
AE	20.5	13.3
Refusal	9.1	11.7
Other	5.3	5.0


Number of patients
HR (95% CI)
Gender
Male
103
0.60 (0.39–0.95)
Female
99
0.60 (0.37–0.99)
Age group
<65 years
136
0.59 (0.39–0.90)
≥65 years
66
0.66 (0.37–1.16)
Race group
Eastern Asian
82
0.67 (0.39–1.15)
Caucasian
77
0.47 (0.27–0.82)
Baseline ECOG PS
0
61
0.64 (0.31–1.30)
1
123
0.71 (0.47–1.06)
2
18
0.45 (0.15–1.30)
Smoking history
Never smoked
108
0.60 (0.38–0.94)
<15 pack-years and stopped >1 year
24
0.89 (0.31–2.50)
Other current or ex-smoker
70
0.56 (0.31–1.01)
Tumor histology
Adenocarcinoma
174
0.69 (0.49–0.99)
Squamous
17
0.15 (0.03–0.62)
Type of prior EGFR inhibitor treatment
Erlotinib only
143
0.65 (0.45–0.95)
Gefitinib only
48
0.56 (0.25–1.26)
Erlotinib + gefitinib
11
0.42 (0.10–1.74)
Higher clinical enrichment criteria
No
82
0.65 (0.39–1.08)
Yes
120
0.56 (0.36–0.87)
Previous pemetrexed
No
91
0.50 (0.30–0.84)
Yes
111
0.72 (0.47–1.12)
Previous taxane
No
97
0.75 (0.45–1.24)
Yes
105
0.51 (0.32–0.80)
1/16
1/4
1
4
16
← Favors afatinib + paclitaxel
Favors chemotherapy →


A
Afatinib + paclitaxel
≥20% increase (n = 3)
≥0% and <20% increase (n = 23)
>0% and <30% decrease (n = 48)
≥30% and <50% decrease (n = 25)
≥50% decrease (n = 20)
Maximum change from baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
0
20
40
60
80
100
120
140
Patients
B
Chemotherapy
≥20% increase (n = 10)
≥0% and <20% increase (n = 15)
>0% and <30% decrease (n = 18)
≥30% and <50% decrease (n = 4)
≥50% decrease (n = 5)
Maximum change from baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
0
10
20
30
40
50
60
Patients


A
Afatinib (n = 1154)
PFS event, n (%) 992 (86.0)
Median PFS (months) 3.2
Estimated probability of PFS
Time from treatment start (months)
Number of patients at risk
1154 517 229 130 70 44 29 21 15 11 5 4 3 0
C
Positive (n = 596)
Negative (n = 558)
PFS event, n (%) 502 (84.2) 490 (87.8)
Median PFS (months) 4.1 2.8
Estimated probability of PFS
Time from treatment start (months)
Number of patients at risk
No 558 203 82 38 18 13 8 8 4 3 0 0 0 0
Yes 596 314 147 92 52 31 21 13 11 8 5 4 3 0
B
Positive (n = 54)
Negative (n = 36)
PFS event, n (%) 48 (88.9) 25 (69.4)
Median PFS (months) 4.0 2.6
Estimated probability of PFS
Time from treatment start (months)
Number of patients at risk
Negative 36 7 1 0 0 0 0 0 0 0 0 0 0 0
Positive 54 25 15 7 5 3 2 2 2 2 1 1 0 0
D
Squamous (n = 90)
Adeno (n = 985)
PFS event, n (%) 76 (84.1) 849 (86.2)
Median PFS (months) 3.7 3.2
Estimated probability of PFS
Time from treatment start (months)
Number of patients at risk
Group 1 985 448 205 120 64 38 23 19 14 10 5 4 3 0
Group 2 90 43 13 7 4 4 4 2 1 1 0 0 0 0


Afatinib + paclitaxel (n = 130)
Chemotherapy (n = 58)
Patients (%)
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
≥Number of subsequent lines of therapy

Supplementary Methods S1. Assessments of quality of life (QoL)

QoL was measured with EQ-5D health status self-assessment questionnaire; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30); EORTC lung cancer-specific supplementary module (QLQ-LC13). Cough (Q1 of QLQ-LC13), dyspnea (Q3 and Q5 of QLQ-LC13), and pain (Q9 and Q19 of QLQ-C30) were assessed per standard published EORTC algorithms. Time-to-deterioration was defined as time from randomization to first 10-point worsening from baseline score.