

**Table S1** Clinical characteristics of adenocarcinoma patients with *EGFR* and *ALK* data

Parameters	Total	<i>EGFR</i> and <i>ALK</i> wild type	<i>EGFR</i> or <i>ALK</i> mutant patients	P value
Total	3,454 (100.0)	1,873 (54.2)	1,581 (45.8)	
Age (years)	66.9±11.6	68.1±10.9	65.5±12.3	<0.001
Sex				
Male	2,061 (59.7)	1,376 (73.5)	685 (43.3)	<0.001
Female	1,393 (40.3)	497 (26.5)	896 (56.7)	<0.001
BMI (kg/m <sup>2</sup> )	23.0±3.4	22.9±3.4	23.3±3.4	0.001
<i>EGFR</i> mutation <sup>†</sup>				<0.001
Exon 19 deletion	253 (7.3)		253 (16.0)	
Exon 21 L858R mutation	197 (5.7)		197 (12.5)	
Other mutations	61 (1.8)		61 (3.9)	
<i>ALK</i> mutation				
<i>ALK</i> IHC (+)	194 (5.6)		194 (12.3)	<0.001
<i>ALK</i> FISH (+)	161 (4.7)		161 (10.2)	<0.001
Smoking status				<0.001
Never	1,628 (47.1)	638 (34.1)	990 (62.6)	
Current	924 (26.8)	658 (35.1)	266 (16.8)	
Ex-smoker	855 (24.8)	551 (29.4)	304 (19.2)	
Unknown	47 (1.4)	26 (1.4)	21 (1.3)	
ECOG				<0.001
0	759 (22.0)	371 (19.8)	388 (24.5)	
1	1,461 (42.3)	768 (41.0)	693 (43.8)	
2	270 (7.8)	165 (8.8)	105 (6.6)	
3	111 (3.2)	68 (3.6)	43 (2.7)	
4–5	40 (1.2)	26 (1.4)	14 (0.9)	
Unknown	813 (23.5)	475 (25.4)	338 (21.4)	
T stage (clinical)				<0.001
Tx	17 (0.5)	9 (0.5)	8 (0.5)	
T1a	87 (2.5)	43 (2.3)	44 (2.8)	
T1b	194 (5.6)	94 (5.0)	100 (6.3)	
T1c	98 (2.8)	41 (2.2)	57 (3.6)	
T1 NOS	43 (1.2)	21 (1.1)	22 (1.4)	
T2a	488 (14.1)	226 (12.1)	262 (16.6)	
T2b	209 (6.1)	107 (5.7)	102 (6.5)	
T2 NOS	165 (4.8)	86 (4.6)	79 (5.0)	
T3	535 (15.5)	315 (16.8)	220 (13.9)	
T4	1,047 (30.3)	591 (31.6)	456 (28.8)	
Unknown	571 (16.5)	340 (18.2)	231 (14.6)	

Table S1 (continued)

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Parameters	Total	<i>EGFR</i> and <i>ALK</i> wild type	<i>EGFR</i> or <i>ALK</i> mutant patients	P value
N stage (clinical)	n=3,348	n=1,818	n=1,530	0.133
N0	561 (16.8)	290 (16.0)	271 (17.7)	
N1	220 (6.6)	111 (6.1)	109 (7.1)	
N2	779 (23.3)	414 (22.8)	365 (23.9)	
N3	1,788 (53.4)	1,003 (55.2)	785 (51.3)	
M status				0.283
M1a	1,007 (29.2)	553 (29.5)	454 (28.7)	
M1b	1,864 (54.0)	1,025 (54.7)	839 (53.1)	
M1c	574 (16.6)	290 (15.5)	284 (18.0)	
M1 NOS	9 (0.3)	5 (0.3)	4 (0.3)	
Intrathoracic metastasis				
MPE	1,036 (30.0)	548 (29.3)	488 (30.9)	0.304
Malignant pericardial effusion	130 (3.8)	76 (4.1)	54 (3.4)	0.323
Pleural nodule	580 (16.8)	285 (15.2)	295 (18.7)	0.007
Contralateral lung	943 (27.3)	502 (26.8)	441 (27.9)	0.473
Extrathoracic site				
Bone	1,593 (46.1)	824 (44.0)	769 (48.6)	0.006
Extra thoracic LN	435 (12.6)	259 (13.8)	176 (11.1)	0.017
Brain	1,072 (31.0)	488 (26.1)	584 (36.9)	<0.001
Adrenal	466 (13.5)	320 (17.1)	146 (9.2)	<0.001
Liver	434 (12.6)	241 (12.9)	193 (12.2)	0.560
Other sites	233 (6.7)	150 (8.0)	83 (5.2)	0.001
Number of distant metastatic sites				0.519
0	1,018 (29.5)	560 (29.9)	458 (29.0)	
1	1,256 (36.4)	689 (36.8)	567 (35.9)	
2 or more	1,180 (34.2)	624 (33.3)	556 (35.2)	

Data are presented as n (%) or mean  $\pm$  standard deviation. <sup>†</sup>, *EGFR* mutation subtypes are analyzed only in patients with regarding data. Some patients do not have data on *EGFR* mutation type. *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; BMI, body mass index; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; MPE, malignant pleural effusion; LN, lymph node.

**Table S2** Comparison of clinical outcomes

Parameters	Total	<i>EGFR</i> or <i>ALK</i> wild type	<i>EGFR</i> or <i>ALK</i> mutant	P value
Total	3,454 (100.0)	1,873 (54.2)	1,581 (45.8)	
Observation time				<0.001
OS (months)				
Mean (SE)	20.8 (0.35)	14.6 (0.39)	28.2 (0.55)	
Median (95% CI)	13.6 (12.8–14.5)	8.0 (7.4–8.6)	24.5 (22.7–26.2)	
Survival rate				
6-month	0.70	0.59	0.86	
12-month	0.52	0.38	0.72	
24-month	0.33	0.20	0.51	
Treatment modality underwent				
Surgery	163 (4.7)	74 (4.0)	89 (5.6)	0.020
RT	1,406 (40.7)	699 (37.3)	707 (44.7)	<0.001
Systemic therapy	2,496 (72.3)	1,168 (62.4)	1,328 (84.0)	<0.001
Supportive care only	373 (10.8)	274 (14.6)	99 (6.3)	<0.001
Underwent RT treatment				
Received RT to lung lesion	246 (7.1)	152 (8.1)	94 (5.9)	0.014
Received RT to extrathoracic metastatic lesion	1,298 (37.6)	622 (33.2)	676 (42.8)	<0.001
Receiving RT to metastatic lesions at				
Bone	599 (17.3)	278 (14.8)	321 (20.3)	<0.001
Extra thoracic LN	10 (0.3)	9 (0.5)	1 (0.1)	0.023
Brain	645 (18.7)	291 (15.5)	354 (22.4)	<0.001
Adrenal	7 (0.2)	5 (0.3)	2 (0.1)	0.360
Liver	4 (0.1)	0 (0.0)	4 (0.3)	0.029

Data are presented as n (%), unless otherwise stated. *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; OS, overall survival; SE, standard error; CI, confidence interval; RT, radiotherapy; LN, lymph node.

**Table S3** Comparison of OS by presence of metastatic lesion in adenocarcinoma

Organs	OS, months [median (95% CI)]		P value
	Group with absent regarding metastases	Group with present regarding metastases	
<i>EGFR</i> and <i>ALK</i> (-) adenocarcinoma			
Brain	8.1 (7.4–8.8)	7.7 (6.5–8.8)	0.304
Bone	10.1 (9.0–11.1)	5.8 (5.0–6.6)	<0.001
Liver	8.7 (8.0–9.4)	4.5 (3.8–5.2)	<0.001
Adrenal	9.0 (8.3–9.7)	4.6 (4.0–5.2)	<0.001
<i>EGFR</i> or <i>ALK</i> (+) adenocarcinoma			
Brain	27.1 (24.3–29.9)	22.3 (20.3–24.3)	<0.001
Bone	32.3 (29.4–35.2)	19.2 (17.0–21.4)	<0.001
Liver	27.1 (25.0–29.2)	13.1 (11.0–15.2)	<0.001
Adrenal	26.2 (24.2–28.3)	13.4 (11.7–15.0)	<0.001
Adenocarcinoma total			
Brain	12.4 (11.5–13.3)	13.9 (12.6–15.2)	0.830
Bone	16.3 (15.0–17.6)	10.1 (9.3–10.9)	<0.001
Liver	14.3 (13.4–15.2)	7.4 (6.2–8.5)	<0.001
Adrenal	14.5 (13.6–15.4)	6.1 (5.2–6.9)	<0.001

Survival comparison was performed using univariate analysis. OS, overall survival; CI, confidence interval; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase.

**Table S4** OS analyses in adenocarcinoma

Parameters	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender				
Female	1		1	
Male	1.46 (1.36–1.57)	<0.001	1.35 (1.13–1.61)	0.001
Age at diagnosis	1.03 (1.03–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
BMI	0.94 (0.93–0.95)	<0.001	0.96 (0.94–0.98)	<0.001
Extrathoracic metastases				
0	1		1	
1	1.23 (1.12–1.34)	<0.001	1.33 (1.07–1.66)	0.010
2 or more	1.74 (1.59–1.90)	<0.001	1.67 (1.25–2.23)	0.001
<i>EGFR</i> mutation				
Negative	1		1	
Positive	0.54 (0.50–0.58)	<0.001	0.50 (0.43–0.57)	<0.001
<i>ALK</i> mutation (IHC or FISH)				
Negative	1		1	
Positive	0.60 (0.51–0.70)	<0.001	0.48 (0.39–0.60)	<0.001
Brain metastases				
None	1		1	
Yes	1.01 (0.93–1.09)	0.830	1.17 (0.98–1.39)	0.077
Liver metastases				
None	1		1	
Yes	1.75 (1.59–1.94)	<0.001	1.42 (1.16–1.74)	0.001
Bone metastases				
None	1		1	
Yes	1.45 (1.35–1.56)	<0.001	1.34 (1.13–1.60)	0.001
RT to lung lesion				
None	1		1	
Received RT	0.75 (0.65–0.86)	<0.001	0.80 (0.64–0.99)	0.042
RT to extrathoracic lesion				
None	1		1	
Received RT	0.86 (0.80–0.93)	<0.001	0.82 (0.71–0.94)	0.005
Intrathoracic metastasis (M1a)				
None	1		1	
Yes	0.95 (0.90–1.03)	0.202	1.26 (1.10–1.49)	0.002

**Table S4** (continued)

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Parameters	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Smoking history				
Never	1		1	
Ever	1.39 (1.29–1.49)	<0.001	1.06 (0.89–1.25)	0.539
ECOG				
0–1	1		1	
2 or more	1.49 (1.41–1.57)	<0.001	1.89 (1.59–2.25)	<0.001
T stage				
T1a–T2	1		1	
T3 and T4	1.47 (1.36–1.59)	<0.001	1.23 (1.08–1.39)	0.002
N stage				
N stage 0	1		1	
N stage I	1.21 (1.03–1.43)	0.025	1.17 (0.89–1.54)	0.270
N stage II	1.40 (1.24–1.57)	<0.001	1.51 (1.24–1.85)	<0.001
N stage III	1.71 (1.54–1.90)	<0.001	1.43 (1.19–1.72)	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group.