

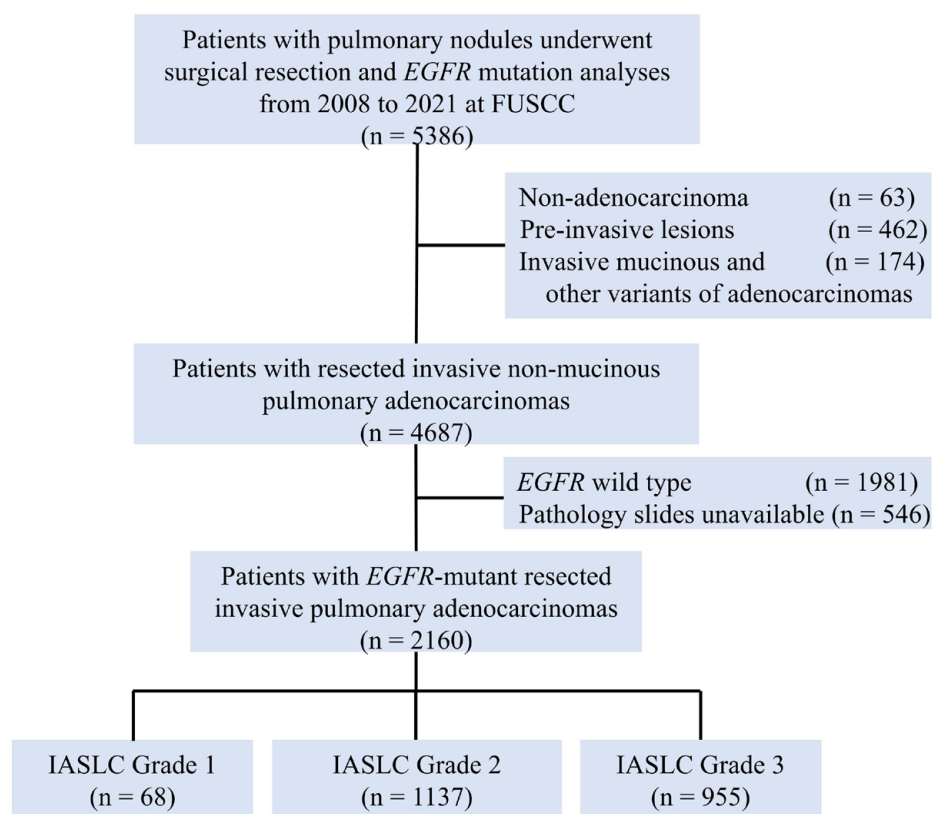


Figure S1 The flowchart of patients enrolled.

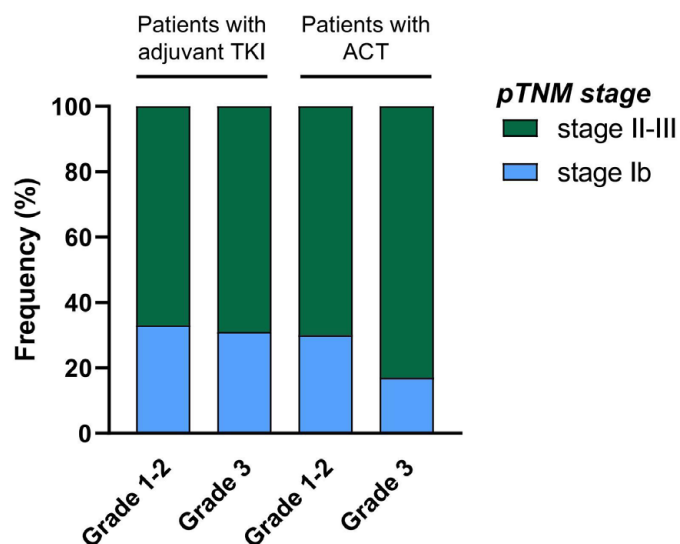


Figure S2 Distribution of pathological stages in each IASLC grades. TKI, tyrosine kinase inhibitor; ACT, adjuvant chemotherapy.

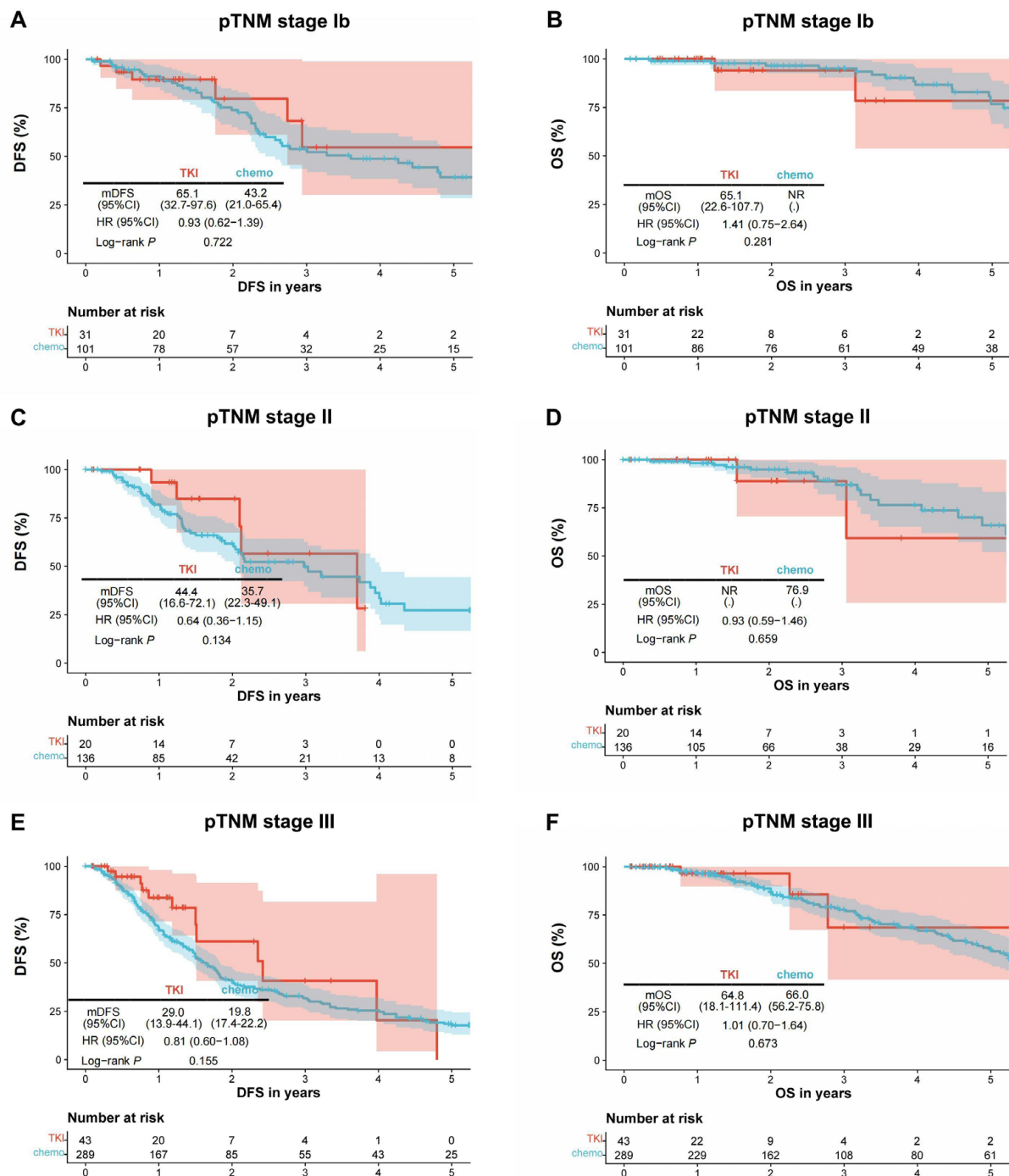


Figure S3 Survival curves for predicting adjuvant EGFR-TKI benefit after tumor resection in pathologic TNM stage I (A,B), stage II (C,D), and stage III (E,F). The 95 % CIs are shown as shaded areas. TKI, tyrosine kinase inhibitor; DFS, disease-free survival; OS, overall survival.

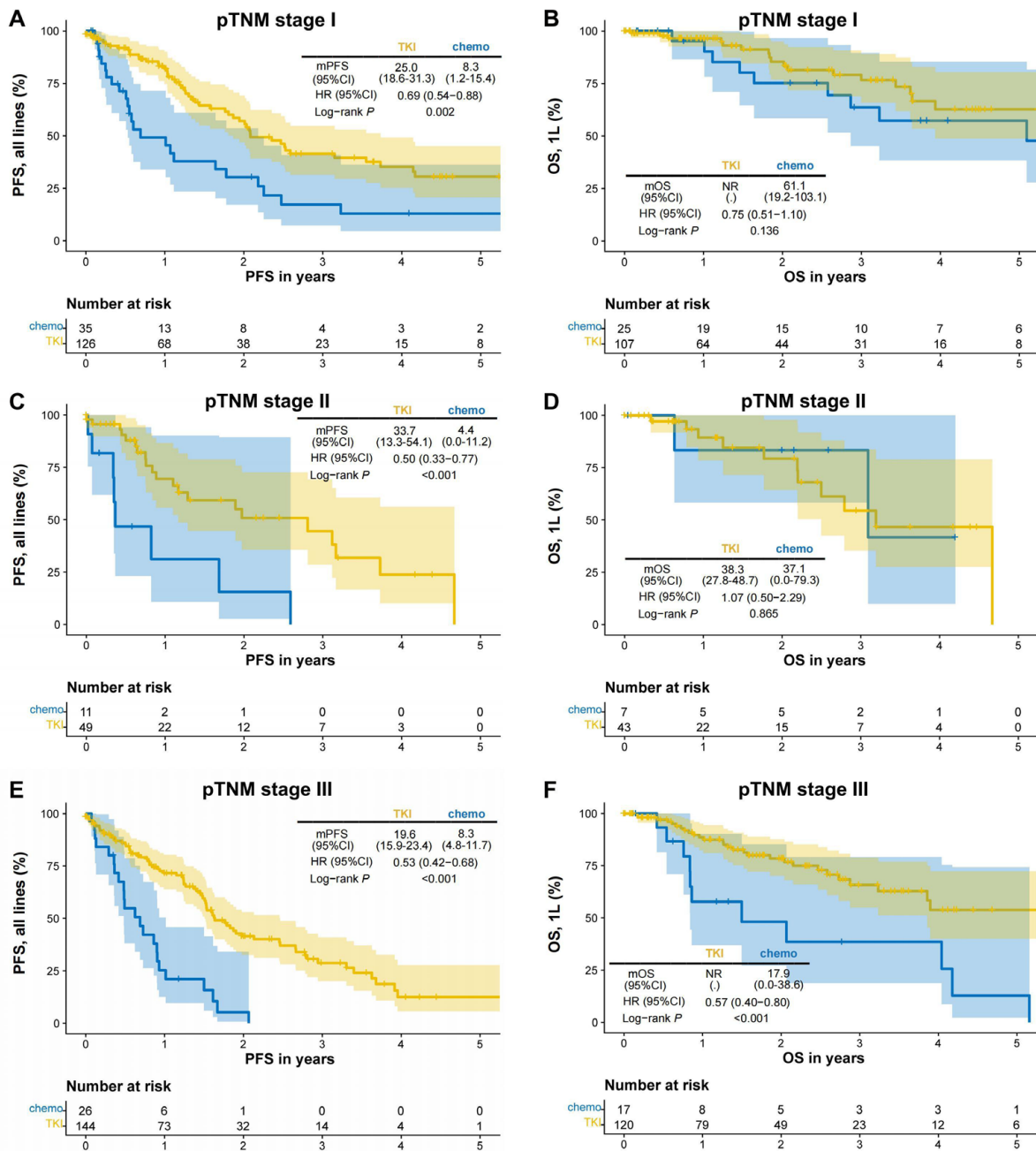


Figure S4 Survival curves for predicting EGFR-TKI benefit after tumor relapse in pathologic TNM stage I (A,B), stage II (C,D) and stage III (E,F). The 95% CIs are shown as shaded areas. TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival.

Table S1 Relationship between IASLC grades and *EGFR* mutations

EGFR mutation types	Total (n=2160)	Grade 1 (n=68)	Grade 2 (n=1137)	Grade 3 (n=955)	P1 ^a	P2 ^b
Exon 19Del	900 (41.7)	27 (39.7)	425 (37.4)	448 (46.9)	<0.001	0.857
Exon 21 L858R	941 (43.6)	30 (44.1)	541 (47.6)	370 (38.7)		
Exon 20ins	94 (4.3)	3 (4.4)	52 (4.6)	39 (4.1)		
Uncommon	116 (5.4)	4 (5.9)	68 (6.0)	44 (4.6)		
T790M	23 (1.1)	1 (1.5)	9 (0.8)	13 (1.3)		
Others	86 (4.0)	3 (4.4)	42 (3.7)	41 (4.3)		

Data are presented as n (%). P1^a, denotes the P value compared of Exon 19Del and Exon 21 L858R. P2^b, denotes the P value compared of classical (19Del + L858R) and other mutations.

Table S2 Relationship between clinicopathologic characteristics and IASLC grading system in the ADJUVANT subgroup (N=620)

Variables	Total (n=620)	Grade 1 (n=4)	Grade 2 (n=116)	Grade 3 (n=500)	P
Age (years)					0.904
Mean	59.6	61.6	59.5	59.6	
SD	9.4	5.1	8.8	9.5	
Gender					0.058
Male	226 (42.9)	1 (25.0)	39 (33.6)	226 (45.2)	
Female	354 (57.1)	3 (75.0)	77 (66.4)	274 (54.8)	
Smoking history					0.214
Never	448 (72.3)	4 (100)	89 (76.7)	355 (71.0)	
Ever	172 (27.7)	0 (0)	27 (23.3)	145 (29.0)	
GGO components ^a					<0.001
Pure-GGO	63 (14.4)	3 (100)	25 (29.4)	35 (10.0)	
Part-solid	7 (1.6)	0 (0)	2 (2.3)	5 (1.4)	
Solid	368 (84.0)	0 (0)	58 (68.2)	310 (88.6)	<0.001
Operative procedure					
Lobectomy	580 (93.6)	4 (100)	97 (83.6)	479 (95.8)	
Segmentation	30 (4.8)	0 (0)	14 (12.1)	16 (3.2)	
Wedge resection	10 (1.6)	0 (0)	5 (4.3)	5 (1.0)	0.004
p-TNM stage					
I	132 (21.3)	2 (50.0)	35 (30.2)	95 (19.0)	
II	156 (25.2)	1 (25.0)	36 (31.0)	119 (23.8)	
III	332 (53.5)	1 (25.0)	45 (38.8)	286 (57.2)	0.257
VPI					
Present	226 (36.5)	1 (25.0)	35 (30.2)	190 (38.0)	
Absent	394 (63.5)	3 (75.0)	81 (69.8)	310 (62.0)	0.003
LVI					
Present	318 (51.3)	2 (50.0)	43 (37.1)	273 (54.6)	
Absent	302 (48.7)	2 (50.0)	73 (62.9)	227 (45.4)	0.020
Adjuvant therapy					
Chemotherapy	526 (84.8)	4 (100)	89 (76.7)	433 (86.6)	
TKI	94 (15.2)	0 (0)	27 (23.3)	67 (13.4)	

Data are presented as n (%) unless otherwise specified. ^a, data were available for a portion of cases. GGO, ground-glass opacity; LVI, lymphovascular invasion; TKI, tyrosine kinase inhibitor; VPI, visceral pleural invasion.

Table S3 Cox regression analysis of DFS in patients with p-TNM stage II-III lung adenocarcinomas (N=488)

Variable	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age (≥60 vs. <60 years)	0.923 (0.723, 1.178)	0.518		
Gender (female vs. male)	1.050 (0.820, 1.345)	0.698		
Smoking history (never vs. ever)	0.984 (0.746, 1.296)	0.906		
GGO components (presence vs. absence)	0.454 (0.277, 0.742)	0.002	0.485 (0.295, 0.798)	0.004
Operative procedure (sublobar vs. lobectomy)	0.646 (0.319, 1.310)	0.226		
IASLC grade (3 vs. 1-2)	1.168 (0.837, 1.631)	0.361		
LVI (presence vs. absence)	1.203 (0.941, 1.539)	0.141		
VPI (presence vs. absence)	1.163 (0.906, 1.493)	0.236		
Adjuvant therapy (TKI vs. chemotherapy)	0.561 (0.332, 0.947)	0.030	0.803 (0.616, 1.045)	0.103
EGFR mutation subtypes				
Exon 19 deletions	Ref.	>0.99		
Exon 21 L858R	0.974 (0.748, 1.267)	0.842		
Atypical	0.948 (0.637, 1.409)	0.790		

DFS, disease-free survival; GGO, ground-glass opacity; IASLC, International Association for the Study of Lung Cancer; LVI, lymphovascular invasion; VPI, visceral pleural invasion.

Table S4 Relationship between clinicopathologic characteristics and IASLC grading system in the RECURRENCE subgroup (N=319)

Variables	Total (n=319)	Grade 1 (n=7)	Grade 2 (n=73)	Grade 3 (n=239)	P
Age (years)					0.318
Mean	59	64	59.5	58.7	
SD	9.6	3.2	9.3	9.8	
Gender					0.575
Male	135 (42.3)	3 (42.9)	27 (37.0)	105 (43.9)	
Female	184 (57.7)	4 (57.1)	46 (63.0)	134 (56.1)	
Smoking history					0.548
Never	234 (73.4)	6 (85.7)	56 (76.7)	172 (72.0)	
Ever	85 (26.6)	1 (14.3)	17 (23.3)	67 (28.0)	
GGO components ^a					<0.001
Pure-GGO	30 (14.4)	3 (100)	12 (31.6)	15 (10.1)	
Part-solid	2 (1.6)	0 (0)	1 (2.6)	1 (0.7)	
Solid	158 (84.0)	0 (0)	25 (65.8)	133 (89.3)	
p-TNM stage					0.002
I	132 (41.4)	4 (57.1)	45 (61.6)	83 (34.7)	
II	50 (15.7)	1 (14.3)	7 (9.6)	42 (17.6)	
III	137 (42.9)	2 (28.6)	21 (28.8)	114 (47.7)	
VPI					0.319
Present	103 (32.3)	1 (14.3)	20 (27.4)	82 (34.3)	
Absent	216 (67.7)	6 (85.7)	53 (72.6)	157 (65.7)	
LVI					0.002
Present	132 (41.4)	3 (42.9)	17 (23.3)	112 (46.9)	
Absent	187 (58.6)	4 (57.1)	56 (76.7)	127 (53.1)	
Therapy					0.221
Chemotherapy	49 (15.4)	0 (0)	15 (20.5)	34 (14.2)	
TKI	270 (84.6)	7 (100)	58 (79.5)	205 (85.8)	

Data are presented as n (%) unless otherwise specified. ^a, data were available for a portion of cases. GGO, ground-glass opacity; LVI, lymphovascular invasion; TKI, tyrosine kinase inhibitor; VPI, visceral pleural invasion.

Table S5 Progression-free and overall survival calculated from Kaplan-Meier plots

Survival category	Stratification	Therapy	No. of treatments	mPFS in months	95% CI	Log-rank (TKI vs. chemo)
All lines PFS	The entire subgroup	TKI	319	23.7	19.1–28.2	<0.001
		Chemo	72	8.3	5.0–11.6	
	IASLC Grade 1-2	TKI	77	21.2	14.7–27.6	<0.001
		Chemo	19	8.3	3.2–13.4	
	IASLC Grade 3	TKI	242	23.7	14.7–27.6	<0.001
		Chemo	52	8.3	4.0–12.5	
1L PFS	The entire subgroup	TKI	270	24.4	18.8–29.9	<0.001
		Chemo	49	10.3	4.8–15.9	
	IASLC Grade 1-2	TKI	65	24.1	7.4–40.9	0.004
		Chemo	15	8.3	0–17.3	
	IASLC Grade 3	TKI	205	24.8	18.2–31.4	<0.001
		Chemo	34	10.3	3.3–17.4	
1L OS	The entire subgroup	TKI	270	NR		0.008
		Chemo	49	48.5	32.3–64.7	
	IASLC Grade 1-2	TKI	65	NR		0.113
		Chemo	15	37.1	25.3–48.9	
	IASLC Grade 3	TKI	205	56.0		0.034
		Chemo	34	38.7	7.7–69.7	