Figure S1. Flow chart showing patient sample availability (black) and respective analyses (blue). *MET*Δex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; PD, progressive disease; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor.

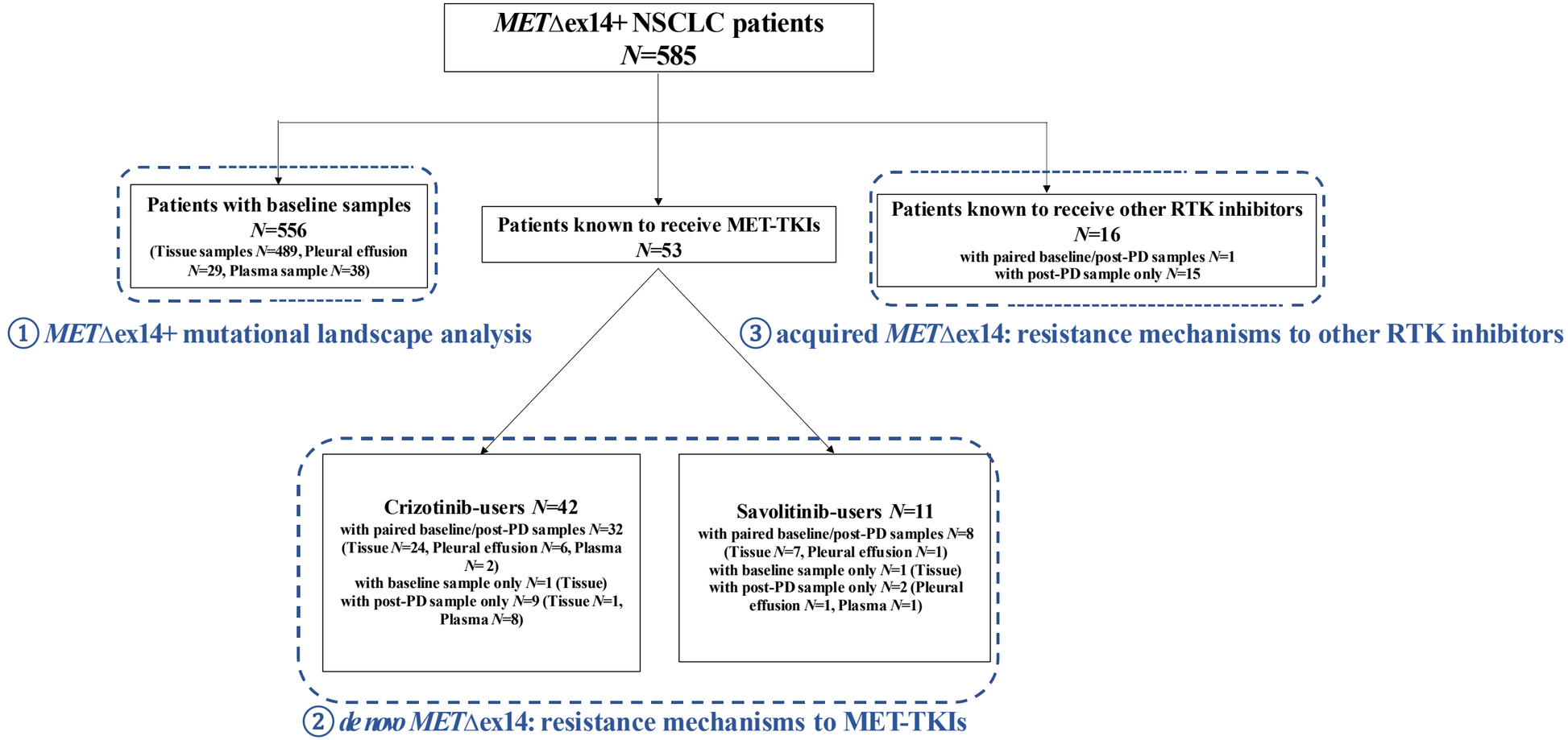


Figure S2. Other baseline genomic characteristics observed in the 556 *MET*Δex14+ patients. (A) Co-occurrence or mutual exclusivity between baseline concurrent alterations. **(B)** Differential prevalence of *CDK4* amplification in the studied population, as grouped by patients' tumor histological types. **(C-D)** Different TMB (C) and CIS (D) levels in patients with or without concurrent *MET* amplification. CIS, chromosomal instability; TMB, tumor mutation burden.

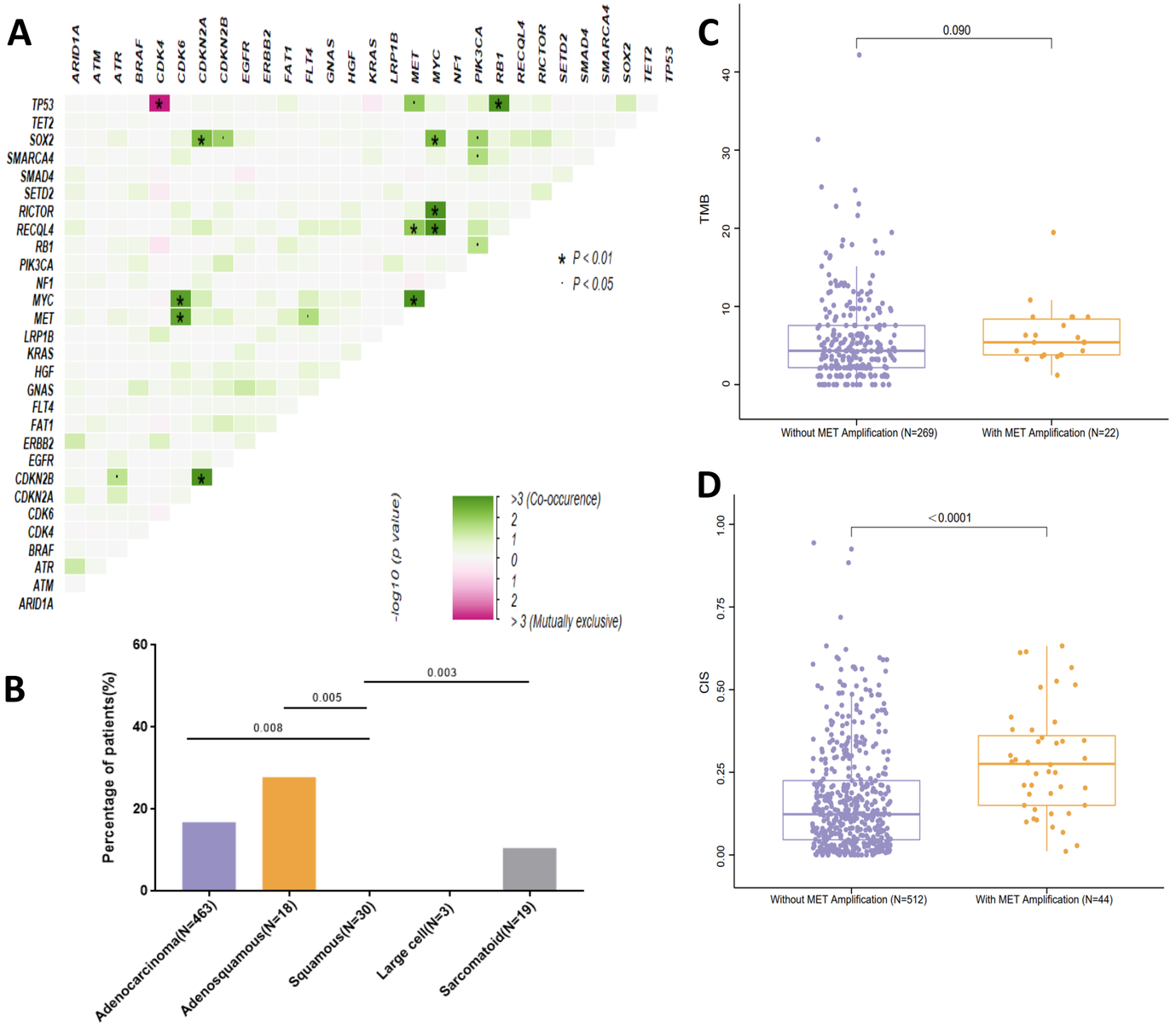
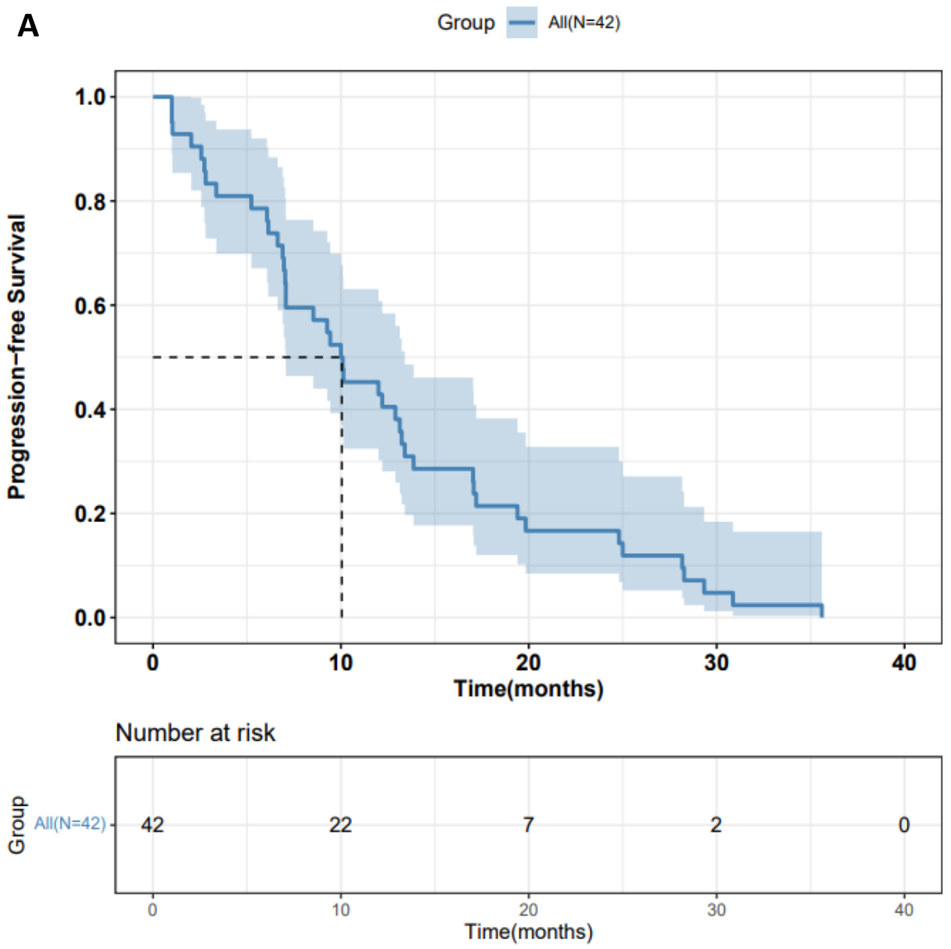


Figure S3. (A) Progression-free survival (PFS) for patients receiving crizotinib (*N*=42) as first-line treatment. (B) PFS for patients receiving savolitinib (*N*=11), among which 8 were treatment-naïve. Median PFS was 10.1 and 10.2 months respectively, as indicated by dashed lines. Pale blue coloring indicated the 95% confidence interval.



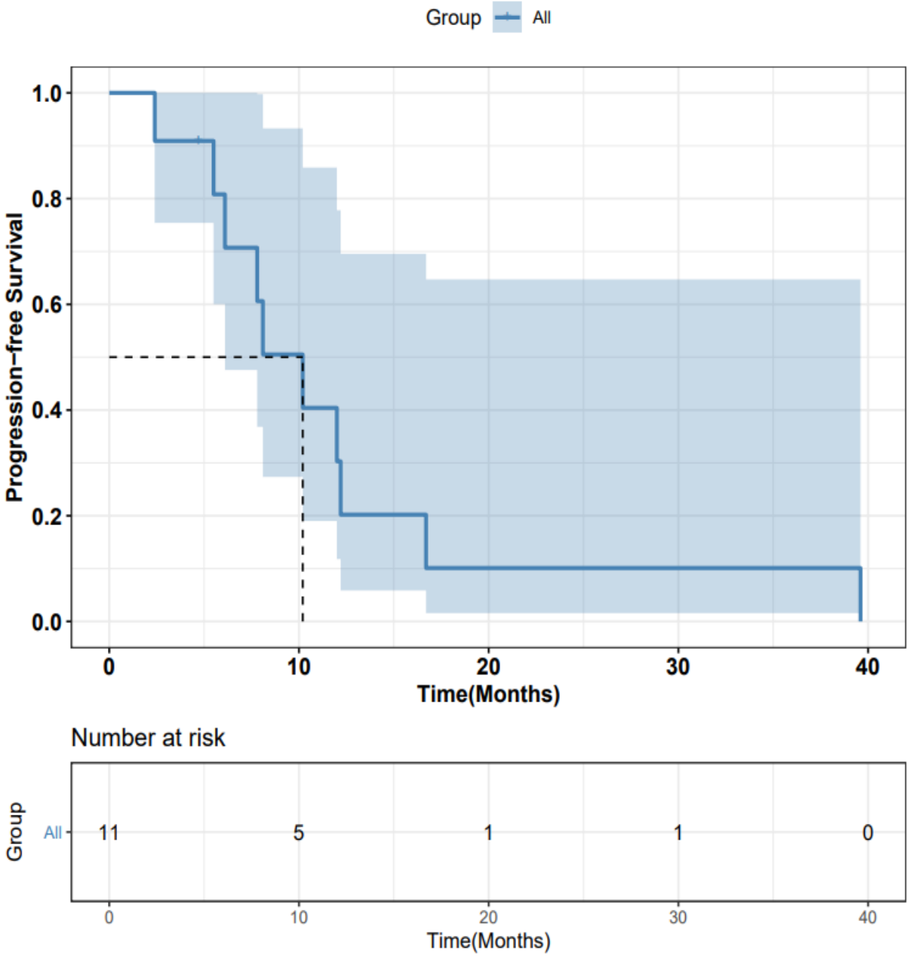


Figure S4. Other *de novo* prognostic markers for crizotinib or savolitinib. (A) Progression-free survival (PFS) in patients with *MET* amplification versus those without. (B) PFS in patients with *MYC* amplification versus wild-type. (C) PFS in patients with *RECQL4* amplification versus wild-type. (D) PFS in patients with alterations in the cell cycle pathway versus those without. (E) PFS in patients with different levels of copy number variation. A copy number ratio > 4.0 or < 0.6 was defined as "High" and the ratio in between 0.6 and 4.0 as "Low". (F) PFS in patients with higher or lower tumor mutation burden (TMB) values as defined by the population's tertile cut-points. Median PFS was indicated by dashed lines. No_amp, no amplification.

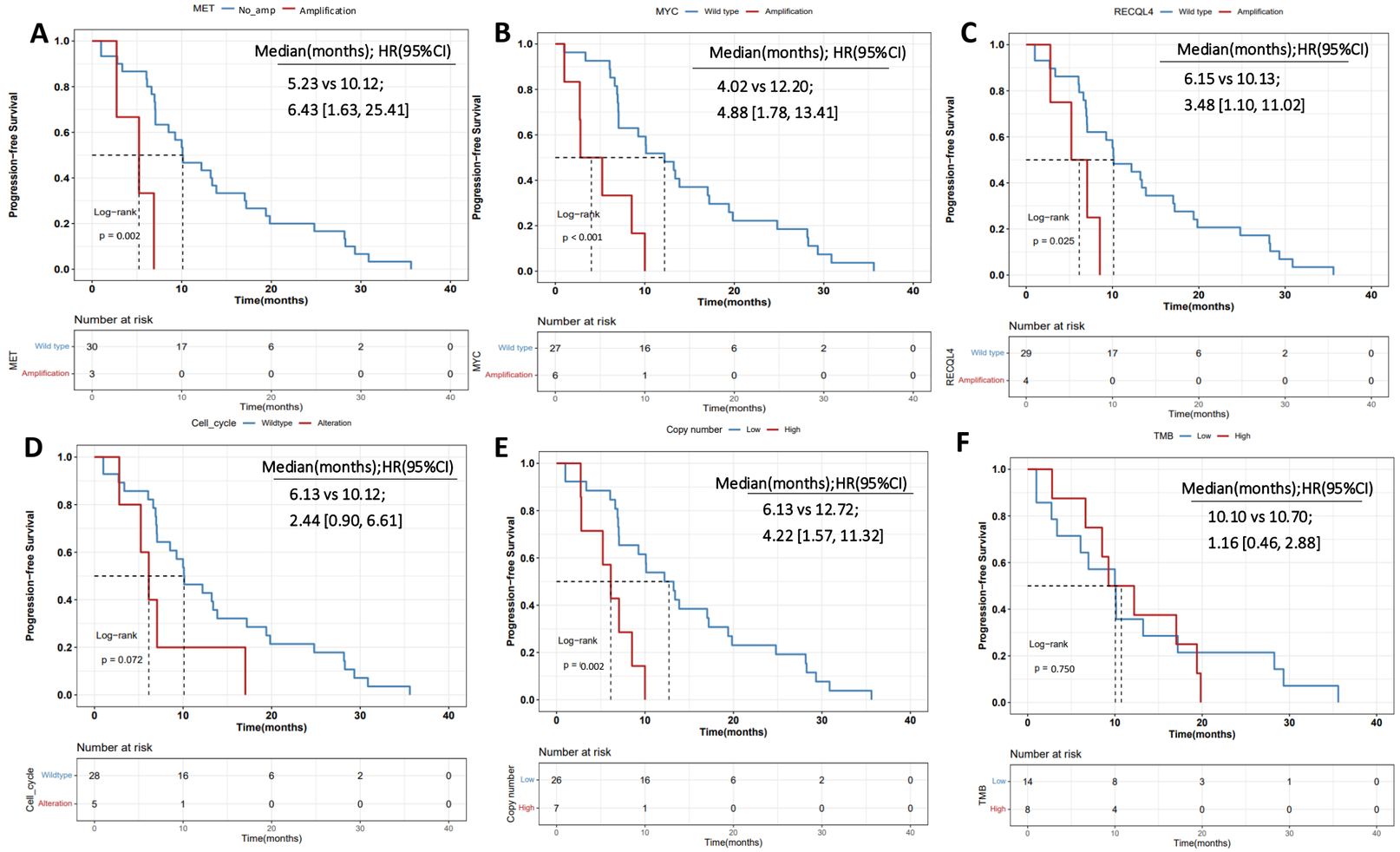


Figure S5. Comparison of mutation frequencies of top occurring genes between tissue and liquid biopsy (plasma/effusion) samples.

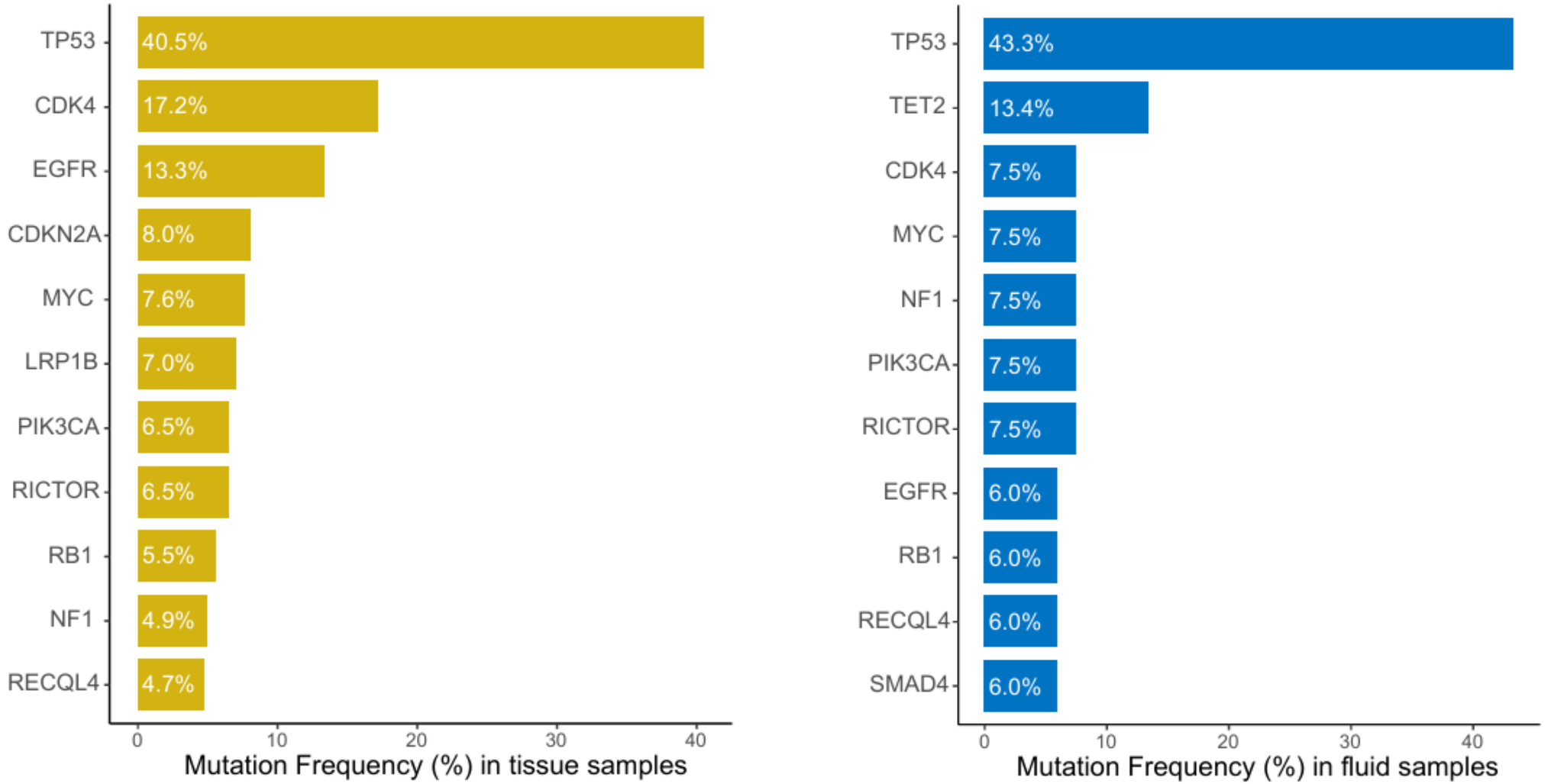


Table S1. The prevalence of *MET* exon 14 skipping mutations in all screened non-small cell lung cancer patients, grouped by their tumor histological types. *MET*Δex14, *MET* exon 14 skipping mutation.

Histological type	All (*N*=57521)	*MET*Δex14+ (*N*=585)	Prevalence	*P*-value
Adenocarcinoma	37513 (84.5%)	486 (87.2%)	1.3%	**< 0.0001**
Adenosquamous	449 (1.0%)	18 (3.2%)	4.0%	
Squamous	6006 (13.5%)	31 (5.6%)	0.5%	
Large cell	252 (0.6%)	3 (0.5%)	1.2%	
Sarcomatoid	196 (0.4%)	19 (3.4%)	9.7%	
Unknown	13105	28		

Table S2. Patient clinical characteristics as grouped by different *MET* exon 14 mutation subtypes. No significant patterns were observed ($P > 0.05$). NSCLC, non-small cell lung cancer; yrs, years.

Characteristics	Base substitution splice acceptor (N=15)	Base substitution splice donor (N=290)	Indel splice acceptor (N=62)	Indel noncoding adjacent splice acceptor (N=132)	Indel splice donor (N=70)	Whole exon 14 deletion (N=8)	D1002/Y1003/ R1004 (N=14)	*P*-value
Median age (range), yrs	61(53-73)	69(44-92)	70.5(47-91)	68(43-91)	69(47-86)	73(50-87)	66.5(33-82)	
Gender, n(%)								**0.423**
Female	8(53.3%)	135(46.6%)	26(41.9%)	66(50.0%)	39(55.7%)	5(62.5%)	4(28.6%)	
Male	7(46.7%)	155(53.4%)	36(58.1%)	66(50.0%)	31(44.3%)	3(37.5%)	10(71.4%)	
Age, n(%)								**0.354**
<69 age, yrs	11(73.3%)	141(48.8%)	27(43.5%)	66(50.4%)	33(47.8%)	2(25.0%)	8(57.1%)	
≥69 age, yrs	4(26.7%)	148(51.2%)	35(56.5%)	65(49.6%)	36(52.2%)	6(75.0%)	6(42.9%)	
Unknown	0	1	0	1	1	0	0	
Histological type of NSCLC, n(%)								**0.716**
Adenocarcinoma	12(80.0%)	248(88.6%)	49(84.5%)	105(86.1%)	57(85.1%)	7(87.5%)	11(84.6%)	
Adenosquamous	0(0.0%)	7(2.5%)	2(3.4%)	7(5.7%)	2(3.0%)	0(0.0%)	0(0.0%)	
Squamous	1(6.7%)	14(5.0%)	6(10.3%)	4(3.3%)	5(7.5%)	0(0.0%)	2(15.4%)	
Large cell	0(0.0%)	1(0.4%)	0(0.0%)	1(0.8%)	1(1.5%)	0(0.0%)	0(0.0%)	
Sarcomatoid	2(13.3%)	10(3.6%)	1(1.7%)	5(4.1%)	2(3.0%)	1(12.5%)	0(0.0%)	
Unknown	0	10	4	10	3	0	1	
Clinical stage, n(%)								**0.702**
I-III	6(54.5%)	63(43.2%)	17(50.0%)	27(38.6%)	13(32.5%)	2(50.0%)	4(50.0%)	
IV	5(45.5%)	83(56.8%)	17(50.0%)	43(61.4%)	27(67.5%)	2(50.0%)	4(50.0%)	
Unknown	4	144	28	62	30	4	6	

Table S3. Clinical and mutational features in patients with or without concurrent *MET* amplification.
NSCLC, non-small cell lung cancer; yrs, years.

Characteristics	Without *MET* Amplification (N=512)	With *MET* Amplification (N=44)	*P*-value
Median age (range), yrs	69(33-92)	71.5(55-91)	
Age, n(%)			**0.208**
<age 69yrs	252(49.5%)	17(38.6%)	
≥age 69yrs	257(50.5%)	27(61.4%)	
Unknown	3	0	
Gender, n(%)			**0.272**
Female	246(48.0%)	17(38.6%)	
Male	266(52.0%)	27(61.4%)	
Type of sample, n(%)			**0.147**
Tissue	447(87.3%)	42(95.5%)	
Body fluids	65(12.7%)	2(4.5%)	
Histological type of NSCLC, n(%)			**0.507**
Adenocarcinoma	426(86.4%)	37(92.5%)	
Adenosquamous	16(3.2%)	2(5.0%)	
Squamous	30(6.1%)	0(0.0%)	
Large cell	3(0.6%)	0(0.0%)	
Sarcomatoid	18(3.7%)	1(2.5%)	
Unknown	19	4	
Stage at diagnosis, n(%)			**0.12**
I-III	127(47.6%)	4(25.0%)	
IV	140(52.4%)	12(75.0%)	
Unknown	245	28	
***MET*Δex14 alterations, n(%)**			**0.749**
Base substitution splice acceptor	12(2.3%)	1(2.2%)	
Base substitution splice donor	252(48.7%)	25(55.6%)	
Indel splice acceptor	53(10.3%)	7(15.6%)	
Indel noncoding adjacent splice acceptor	116(22.4%)	7(15.6%)	
Indel splice donor	63(12.2%)	4(8.9%)	
Whole exon 14 deletion	8(1.5%)	0(0.0%)	
D1002/Y1003/R1004	13(2.5%)	1(2.2%)	

Table S4. Clinical and mutational features in patients with or without concurrent driver mutations. NSCLC, non-small cell lung cancer; yrs, years.

Characteristics	Without Driver (N=514)	With Driver (N=42)	*P*-value
Median age (range), yrs	69(33-92)	66.5(46-84)	
Age, n(%)			**0.427**
<age 69yrs	246(48.1%)	23(54.8%)	
≥age 69yrs	265(51.9%)	19(45.2%)	
Unknown	3	0	
Gender, n(%)			**0.201**
Female	239(46.5%)	24(57.1%)	
Male	275(53.5%)	18(42.9%)	
Type of sample, n(%)			**0.459**
Tissue	450(87.5%)	39(92.9%)	
Body fluids	64(12.5%)	3(7.1%)	
Histological type of NSCLC, n(%)			**0.554**
Adenocarcinoma	424(86.4%)	39(92.9%)	
Adenosquamous	18(3.7%)	0(0.0%)	
Squamous	29(5.9%)	1(2.4%)	
Large cell	3(0.6%)	0(0.0%)	
Sarcomatoid	17(3.5%)	2(4.8%)	
Unknown	23	0	
Stage at diagnosis, n(%)			**1.000**
I-III	117(45.3%)	11(44.0%)	
IV	141(54.7%)	14(56.0%)	
Unknown	256	17	
***MET*Δex14 alterations, n(%)**			**0.077**
Base substitution splice acceptor	10(1.9%)	3(7.1%)	
Base substitution splice donor	255(49.0%)	22(52.4%)	
Indel splice acceptor	55(10.6%)	5(11.9%)	
Indel noncoding adjacent splice acceptor	117(22.5%)	6(14.3%)	
Indel splice donor	64(12.3%)	3(7.1%)	
Whole exon 14 deletion	8(1.5%)	0(0.0%)	
D1002/Y1003/R1004	11(2.1%)	3(7.1%)	

Table S5. Univariate Cox regression analysis of clinical characteristics and genomic alterations associated with PFS in crizotinib-treated patients (N=33). P-values for genomic alterations were adjusted using the False Discovery Rate (FDR) method.

Characteristics	Crizotinib (N=33)	events	HR (95% CI)	P-value	FDR
Age, n (%)				0.976	0.976
<age 65yrs	16 (48.5%)	16 (100.0%)	Reference		
≥age 65yrs	17 (51.5%)	17 (100.0%)	0.99 (0.48~2.02)		
Sex, n(%)				0.519	0.623
Female	21 (63.6%)	21 (100.0%)	Reference		
Male	12 (36.4%)	12 (100.0%)	1.27 (0.61~2.62)		
Histological type of NSCLC,n(%)				0.169	0.225
Non_adenocarcinoma	9 (28.1%)	9 (100.0%)	Reference		
Adenocarcinoma	23 (71.9%)	23 (100.0%)	0.58 (0.26~1.27)		
Unknown	1	1 (100.0%)	-		
Stage at diagnosis, n(%)				-	-
IV	33 (100.0%)	33 (100.0%)	-		
Sample_types, n(%)				0.110	0.165
Non-tissue	8 (24.2%)	8 (100.0%)	Reference		
Tissue	25 (75.8%)	25 (100.0%)	2.22 (0.82-6.00)		
CIS_group, n(%)				0.036	0.086
Low	11 (33.3%)	11 (100.0%)	Reference		
High	22 (66.7%)	22 (100.0%)	2.28 (1.04-5.04)		
ITH_group, n(%)				0.059	0.118
Low	21 (63.6%)	21 (100.0%)	Reference		
High	12 (36.4%)	12 (100.0%)	2.11 (0.96-4.66)		
CYLD, n(%)				0.000	0.004
Wildtype	31 (93.9%)	31 (100.0%)	Reference		
Mutant	2 (6.1%)	2 (100.0%)	12.78 (2.09-78.11)		
MET, n(%)				0.002	0.009
Wildtype	30 (90.9%)	30 (100.0%)	Reference		
Amplification	3 (9.1%)	3 (100.0%)	6.43 (1.63~25.41)		
MYC, n(%)				0.001	0.004
Wildtype	27 (81.8%)	27 (100.0%)	Reference		
Amplification	6 (18.2%)	6 (100.0%)	4.88 (1.78~13.41)		
RECQL4, n(%)				0.024	0.072
Wildtype	29 (87.9%)	29 (100.0%)	Reference		
Amplification	4 (12.1%)	4 (100.0%)	3.48 (1.10~11.02)		
Cell cycle, n(%)				0.070	0.121
Wildtype	28 (84.8%)	28 (100.0%)	Reference		
Alterations	5 (15.2%)	5 (100.0%)	2.44 (0.90~6.61)		

Table S6. Clinical and genomic characteristics of 16 patients who detected *MET*Δex14 following progression on EGFR or ALK inhibitors.

Patient ID	Prior TKI Treatment	Sample Type (at Progression)	METΔex14 Variant (HGVS)	Variant Type	Variant Allele Frequency
P01	Afatinib	Tissue	c.2888-21_2888-3del	Intronic variant	24.47%
P02	Afatinib	Plasma	c.2888-2A>T	Splice acceptor site	8.97%
P03	Gefitinib	Pleural effusion	c.2888-27_2888-16del	Intronic variant	0.26%
P04	Gefitinib	Tissue	c.2888-18_2888-5del	Intronic variant	49.61%
P05	Gefitinib	Plasma	c.3028G>A(p.D1010N)	Missense	2.88%
P06	Gefitinib	Tissue	c.3026_3028+3delAAGGTA	Splice donor site	16.67%
P07	Gefitinib	Plasma	c.2888-23_2895delTCTTTCTTTCTCTCTGTTTTAAGATCTGGGC	Splice acceptor site	0.37%
P08	Erlotinib	Tissue	c.3028G>C(p.D1010H)	Missense	52.99%
P09	Erlotinib	Plasma	c.2888-12_2888-9delCTCT	Intronic variant	2.71%
P10	Icotinib	Tissue	c.3020_3028+2del	Splice donor site	37.05%
P11	Icotinib+Anlotinib	Tissue	c.2888-16_2888-13del	Intronic variant	0.84%
P12	Icotinib	Plasma	c.2888-1G>A	Splice acceptor site	0.37%
P13	Icotinib	Plasma	c.3028G>A(p.D1010N)	Missense	0.64%
P14	Icotinib	Plasma	c.3028+1G>C	Splice donor site	0.77%
P15	Alectinib	Plasma	c.2888-12_2888-9dup	Intronic variant	42.20%
P16	Icotinib	Plasma	c.3028G>T(p.D1010Y)	Missense	0.28%