

**Table S1** The list of 212 genes in the panel

ABL1	CASP8	EPHB2	HDAC6	MAP2K1	PARP3	RET	YY1
ABL2	CDK12	EPHB6	HDAC8	MAP2K2	PARP4	ROS1	ZNF143
ACVR1B	CDK2	ERBB2	HRAS	MAP2K4	PBRM1	RUNX3	
ACVR2A	CDK4	ERBB3	HRH2	MAPK1	PDGFRA	SHC1	
AKT1	CDK6	ERBB4	HSP90AA1	MAPK3	PDGFRB	SMC3	
AKT2	CDK7	ERCC1	HSPA4	MAPK8	PDK1	SOS1	
AKT3	CDK8	ERCC2	IDH1	MAPK8IP1	PIGF	SRC	
ALK	CDKN1A	ERCC3	IDH2	MAX	PIK3C2A	STAT3	
AR	CDKN1B	FGF10	IFNAR1	MAZ	PIK3C2B	STAT4	
ARAF	CDKN2A	FGF12	IFNAR2	MDM2	PIK3C2G	STAT5A	
ARID1A	CDKN2B	FGF14	IGF1	MDM4	PIK3C3	STAT5B	
ARID2	CDKN2C	FGF19	IGF1R	MET	PIK3CA	SYK	
ATM	CEBPB	FGF23	IGF2	MSH6	PIK3CB	TET1	
ATR	CYP2C19	FGF6	IL7R	MTA3	PIK3CG	TET2	
ATRX	CYP2D6	FGF7	ING1	MTOR	PIK3R1	TGFB1	
AURKA	CYP3A4	FGFR1	ING4	MUC1	PIK3R2	TGFBR2	
AURKB	DAG1	FGFR2	JAK1	MXI1	PIM1	TLR4	
AXL	DDR1	FGFR3	JAK2	MYC	PLK1	TNFAIP3	
BAD	DDR2	FGFR4	JAK3	NBN	PML	TNFRSF13B	
BCL2L11	DIRAS3	FLT1	KAT6A	NFKBIA	PRKCA	TNFRSF14	
BCL7A	DNMT1	FLT3	KAT6B	NOTCH1	PRKCB	TNFRSF8	
BHLHE40	DNMT3A	FLT4	KDM5A	NOTCH2	PTEN	TOP1	
BIRC5	DNMT3B	FOXM1	KDM5C	NOTCH3	PTK2	TOP2A	
BRAF	EDNRA	GAB1	KDM6A	NOTCH4	PTK2B	TOP2B	
BRCA1	EGFR	GNRHR	KDR	NRAS	RAD21	TP53	
BRCA2	EPHA2	GRB2	KIT	NTRK1	RARA	TRIM33	
BRD1	EPHA3	HDAC1	KMT2A	NTRK2	RARB	TSHR	
BRD3	EPHA5	HDAC2	KMT2B	NTRK3	RARG	UGT1A1	
BRD4	EPHA7	HDAC3	KMT2C	PARP1	RB1	VEGFA	
BTK	EPHB1	HDAC4	KRAS	PARP2	RCOR1	VEGFB	

**Table S2** PK analysis

Dose (mg)	N	Median, T <sub>max</sub> (h)	Mean (CV%)									Mean ± SD, t <sub>1/2</sub> (h)
			λ <sub>z</sub> (1/h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (h*ng/mL)	AUC <sub>0-24</sub> (h*ng/mL)	AUC <sub>0-inf</sub> (h*ng/mL)	AUC_%Extrap (%)	CL/F (L/h)	V <sub>z</sub> /F (L)	MRT (h)	
Cycle 0 single dose												
150	3	4.00	0.0232 (17.6)	110 (15.0)	2240 (25.8)	1400 (12.4)	2300 (26.5)	2.26 (30.5)	65.3 (26.5)	2810 (17.9)	25.9 (22.8)	30.2±5.34
200	8	3.50	0.0261 (22.5)	220 (32.5)	4590 (30.8)	2600 (26.9)	4700 (31.6)	1.69 (101.5)	42.5 (31.6)	1630 (36.9)	29.1 (18.2)	27.1±6.16
225	19	3.00	0.0246 (21.3)	206 (48.9)	5230 (39.9)	2720 (49.6)	5380 (38.9)	2.19 (81.8)	41.8 (38.9)	1700 (54.4)	31.9 (13.8)	28.8±6.91
250	2	4.00	0.0332	225	4810	3040	4840	0.525	51.7	1560	24.5	21.0
Cycle 1 multiple dose												
150	3	3.00	0.0236 (24.9)	265 (27.5)	98.4 (39.8)	158 (15.0)	3790 (15.0)	105 (12.4)	39.6 (15.0)	1670 (29.8)	2.76 ±0.626	29.9±6.95
200	8	2.00	0.0252 (27.8)	474 (35.7)	184 (60.2)	299 (47.7)	7170 (47.7)	89.4 (47.1)	27.9 (47.7)	1110 (45.7)	3.08 ±1.60	28.4±7.89
225	12	3.00	0.0204 (27.9)	435 (55.6)	190 (90.1)	290 (61.7)	6950 (61.7)	76.8 (48.6)	32.4 (61.7)	1590 (59.0)	3.43 ±2.03	35.4±12.2

**Table S3** Best ORR In All Patients (Cutoff Date: December 31, 2020)

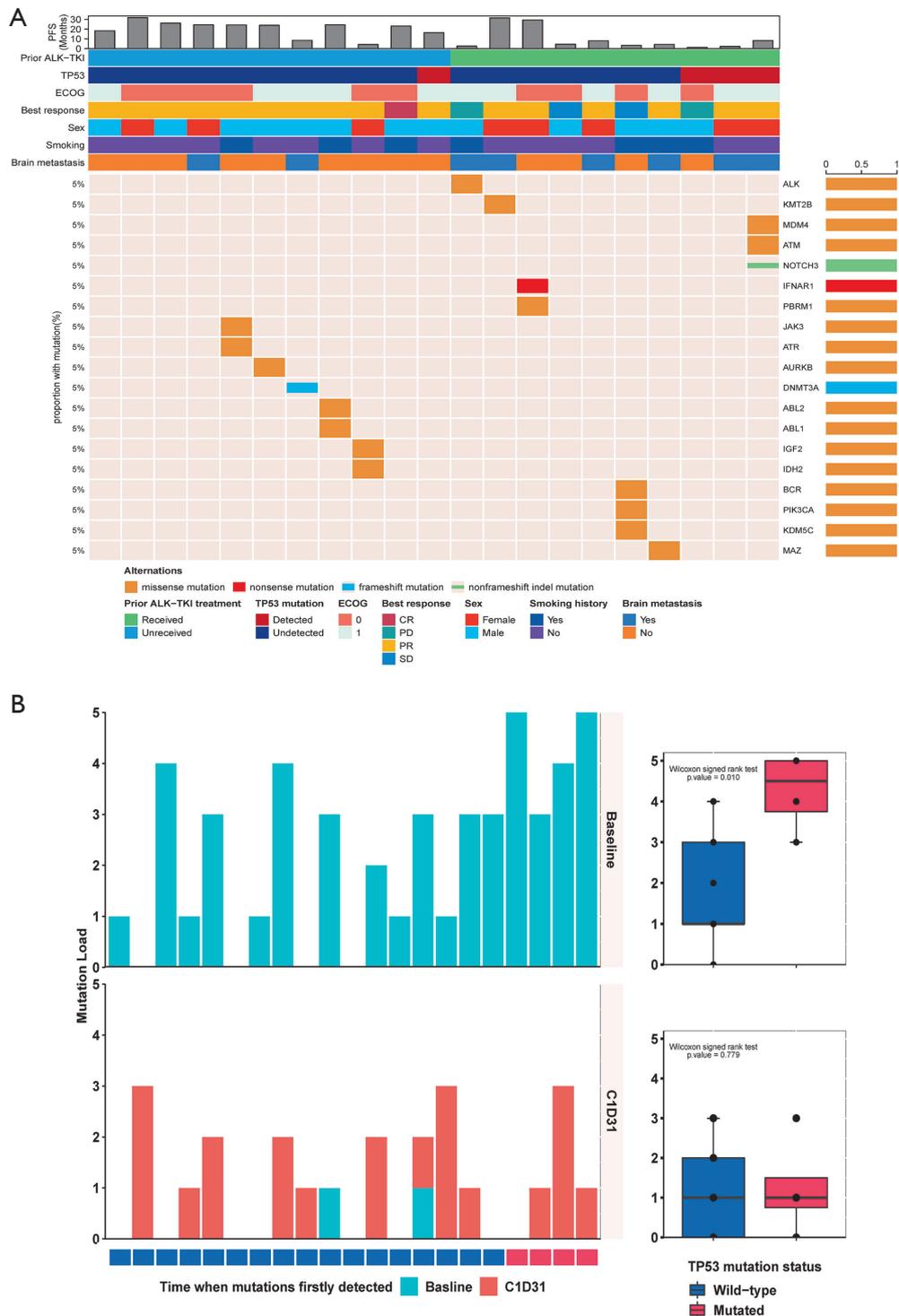
Efficacy	Ensartinib Dose Cohorts(Mg)									
	150 (N=3)		200 (N=8)		225 (N=35)		250 (N=2)		Total (N=48)	
	No.	%	No.	%	No.	%	No.	%	No.	%
CR					1	2.9			1	2.1
PR	1	33.3	7	87.5	20	57.1	2	100	30	62.5
SD, Months										
2-6	1	33.3	1	12.5	2	5.7			4	8.3
≥6					4	11.4			4	8.3
PD	1	33.3			6	17.1			7	14.6
NA					2	5.7			2	4.2
ORR (95% CI)		33.3		87.5	60.0 (42.9 to 77.1)			100	64.6 (50.5 to 78.6)	
DCR (95% CI)		66.7		100	77.1 (62.5 to 91.8)			100	81.3 (69.8 to 92.7)	
CBR (95% CI)		33.3		87.5	71.4 (55.7 to 87.2)			100	72.9 (59.9 to 86.0)	
Median PFS, Months		2.07		26.88	16.62			22.82	16.79	
(95% CI)		(1.15, 16.79)		(2.29 to 51.46)	(7.11 to 26.14)			–	(8.11 to 25.47)	
(Minimum, Maximum)		–		(2.33, 43.17)	(0.46, 36.99)			(18.23, 38.37)	(0.46, 43.17)	
Median OS, Months		–		–	–			–	42.88	
(95% CI)		–		–	–			–	(23.37 to 62.38)	
(Minimum, Maximum)		(21.98, 45.60)		(7.33, 43.17)	(0.53, 40.90)			(27.07, 38.37)	(0.53, 45.60)	

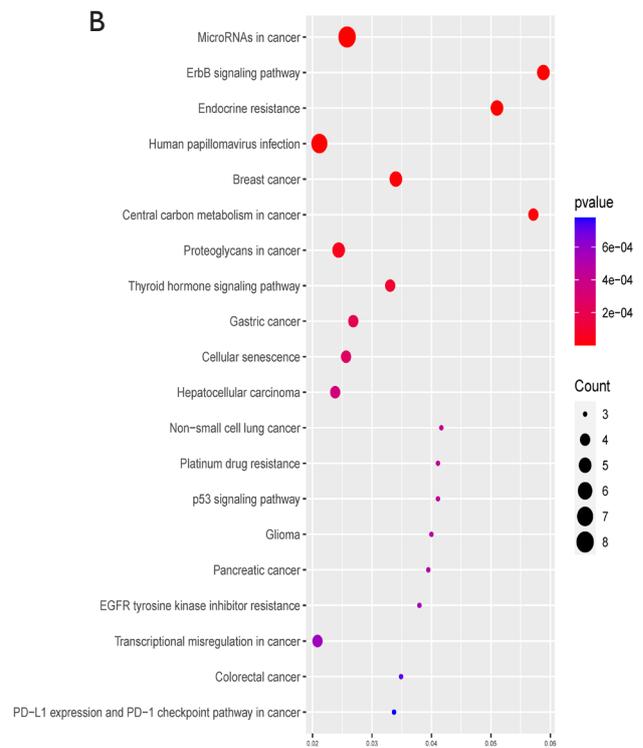
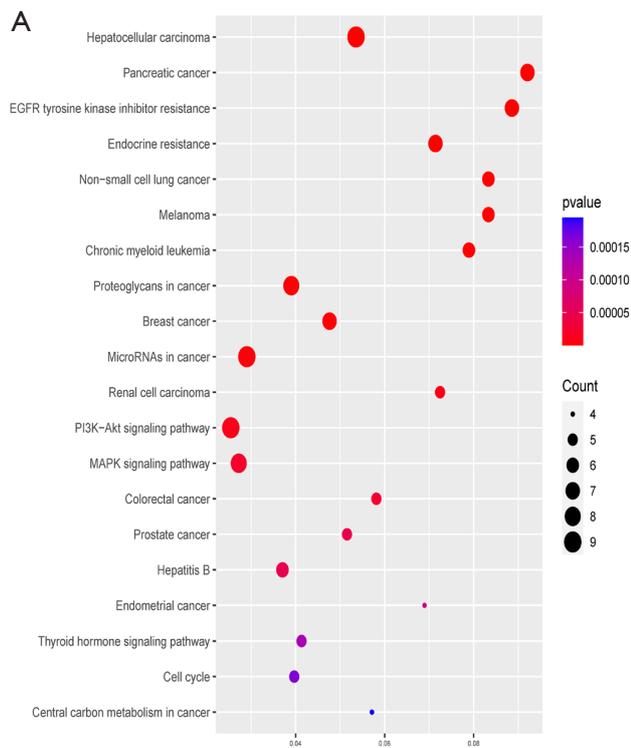
Abbreviations: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; CBR, clinical benefit rate (CR + PR + SD ≥6 Months); ORR, Objective Response Rate (CR + PR); DCR, Disease Control Rate (CR + PR + SD); PFS, Progression-Free Survival; OS, Overall Survival; Month =30.4375 days.

**Table S4** Best ORR In Different Cohorts (Cutoff Date: December 31, 2020)

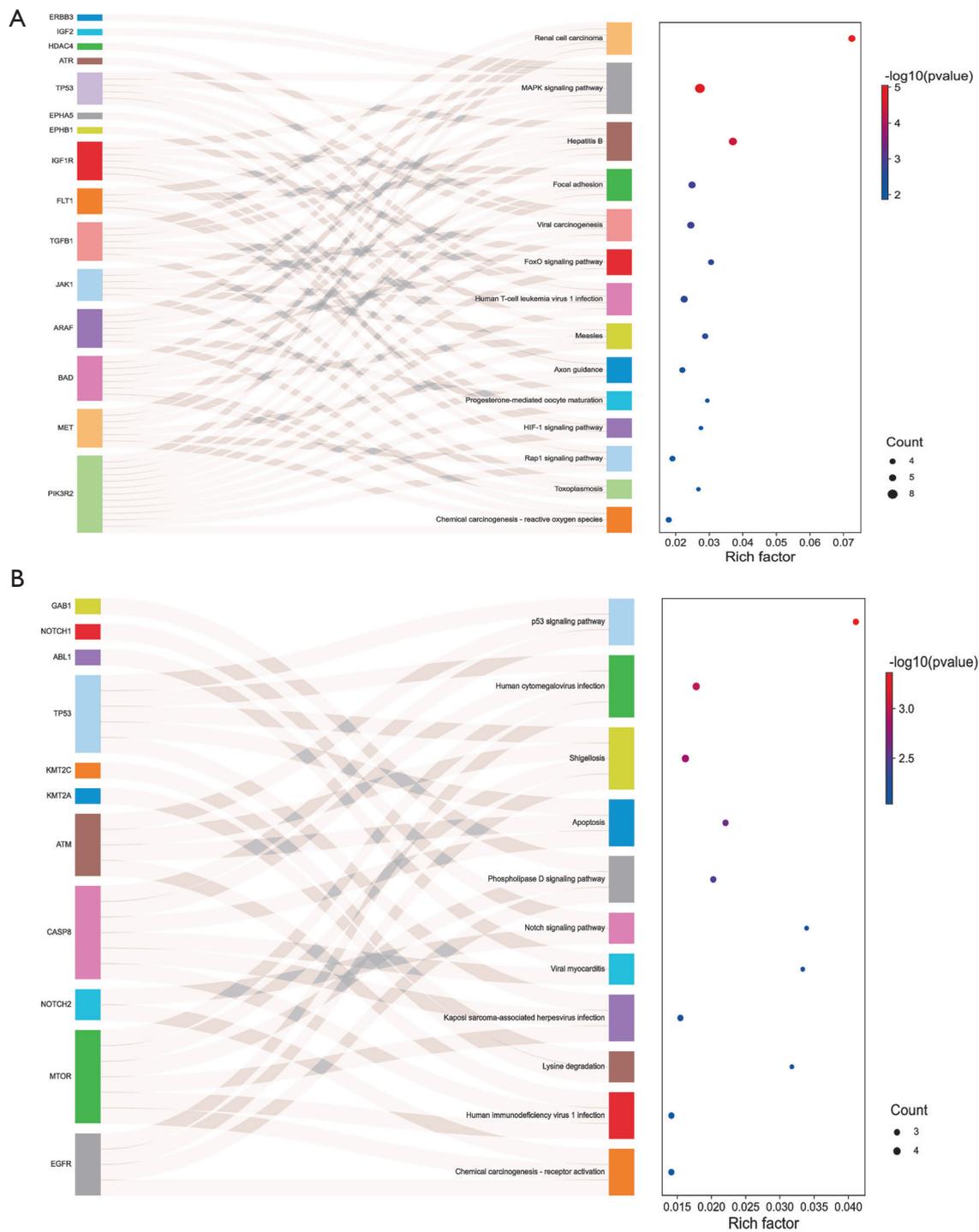
Efficacy	ALK+ (N=43)		ALK + TKI-naïve (N=32)		ALK + TKI-resistance (N=11)		ROS1+ (N =5)		Brain metastasis (N=16)	
	No.	%	No.	%	No.	%	No.	%	No.	%
CR	1	2.3	1	3.1						
PR	30	69.8	25	78.1	5	45.5			11	
SD, months										
2-6	4	9.3			4	36.4			2	
≥6	1	2.3			1	9.1	3	60		
PD	5	11.6	4	12.5	1	9.1	2	40	3	
NA	2	4.7	2	6.3						
ORR (95% CI)	72.1 (58.1 to 86.1)		81.3 (67.0 to 95.5)		45.5 (10.4 to 80.5)		0		68.8 (43.2 to 94.3)	
DCR (95% CI)	83.7 (72.2 to 95.2)		81.3 (67.0 to 95.5)		90.9 (70.7 to 111.2)		60		81.3 (59.8 to 102.7)	
CBR (95% CI)	74.4 (60.8 to 88.0)		81.3 (67.0 to 95.5)		54.5 (19.5 to 89.6)		60		68.8 (43.2 to 94.3)	
Median PFS, Months	18.23		25.73		4.14		8.51		7.59	
(95% CI)	(8.77 to 27.70)		(20.41 to 31.04)		(0.00 to 8.75)		(0.00 to 24.45)		(6.75 to 8.43)	
(Minimum, Maximum)	(0.46, 43.17)		(0.46, 43.17)		(1.15, 41.69)		(0.49, 16.62)		(0.49, 41.69)	
Median OS, Months	42.88		43.17		21.98		16.62		22.34	
(95% CI)	(23.43 to 62.32)		(26.31 to 60.04)		(5.56 to 38.40)		(0.00 to 49.78)		(12.36 to 32.32)	
(Minimum, Maximum)	(6.64, 45.60)		(8.61, 45.60)		(6.64, 42.88)		(0.53, 39.43)		(0.526, 42.88)	

Abbreviations: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; CBR, Clinical Benefit Rate (CR+ PR + SD ≥6 Months); ORR, Objective Response Rate (CR + PR); DCR, Disease Control Rate (CR + PR + SD); PFS, Progression-Free Survival; OS, Overall Survival; Month = 30.4375days.





**Figure S2** KEGG pathway enrichment analysis of genes detected with nonsynonymous mutations in long PFS and short PFS group. The pathway enriched in long PFS group (A) and the pathway enriched in short PFS group (B)



**Figure S3** Specifically enriched pathways in long PFS and short PFS groups. The pathway enriched only in long PFS group but not in short PFS group(A) and the pathway enriched only in short PFS group but not in long PFS group (B).