





P2. 120: Distinct biological characteristics of lung adenocarcinomas according to KRAS mutation subtype

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No conflict of interest to disclose.



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- ✓ KRAS mutations are the most frequent driver oncogenes in human cancers, occurring in approximately 30% and 15% of Western and Asian lung adenocarcinomas (LUADs), respectively.
- ✓ Recently, selective KRAS G12C inhibitors, such as sotorasib and adagrasib, have demonstrated clinical activity.

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Objective

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To elucidate the biological characteristics of KRAS mutation subtypes of LUADs that are necessary for developing new personalized treatments.

Materials and Methods

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- ✓ In total, 1382 surgically resected LUADs were examined for KRAS mutations between February 2010 and July 2016. (PNA-mediated PCR clamping method)
- ✓ Co-occurring mutations were analyzed using next-generation sequencing. (Targeted NGS [Ion AmpliSeq™])

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- ✓ PD-L1 (clone 22C3), PD-L2 (clone 176611), and TTF1 (clone 8G7G3/1) expressions were immunohistochemically evaluated using tissue microarrays.
 - PD-L1 and PD-L2 expression statuses were classified based on the tumor proportion score (TPS) as negative (<1%), weakly positive (1–49%), or strongly positive (≥50%).
 - TTF-1 was considered positive if 1% or greater of tumor cells were stained.
- ✓ The Kaplan-Meier method and log-rank test were used to estimate and compare overall survival (OS) and relapse-free survival (RFS).

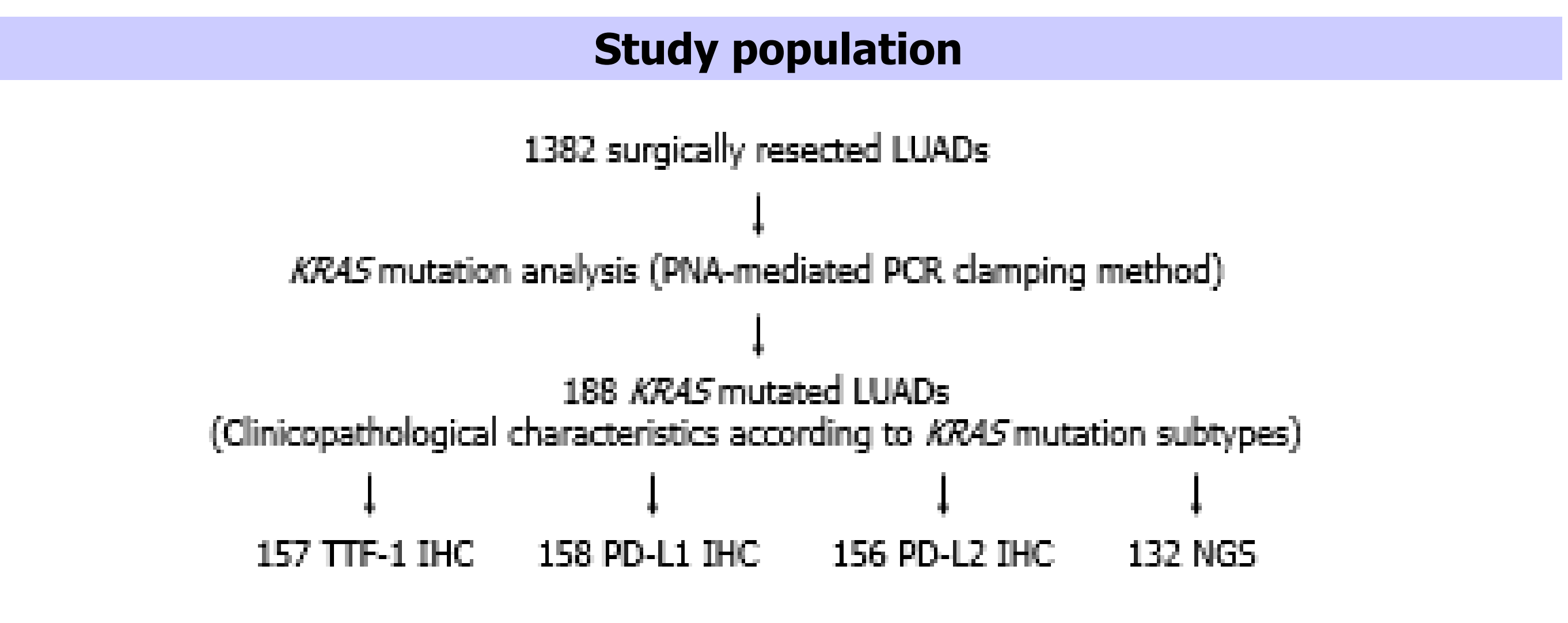
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- ✓ Co-occurring mutations and PD-L1, PD-L2, TTF-1 expression statuses, survival outcomes were compared according to KRAS mutation subtypes.

Study population



Ion AmpliSeq™ (Juntendo Lung Cancer Panel): 74 target genes list

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SFTPB	SOX2	NFE2L2	TP53	ALK
ATM	FGFR3	ASCL4	RASA1	KDM6A
STK11	TERT	NTRK1	POLE	CDK4
MYC	TSC1	RET	SFTPC	ERBB4
AKT2	KMT2D	FGFR2	SMARCA4	SFTPA2
HRAS	NOTCH1	ARID1A	r_TERT	NRAS
TP63	PTEN	MAP2K1	NOTCH2	MDM2
RIT1	ROS1	U2AF1	EGFR	NF1
MGA	MYCN	SETD2	AKT3	FAT1
PIK3CA	AKT1	BRAF	CCND1	SFTPD
SETD1A	KRAS	SFTPA1	CDK6	SOS1
RB1	MCL1	CTNNB1	FOXP1	ERBB3
POLD1	ERBB2	FGFR1	RBM10	NKX2-1
ARID2	SMAD4	ARID1B	TSC2	CUL3
CREBBP	MET	CDKN2A	KEAP1	

Results

Clinical characteristics according to KRAS mutation subtypes of LUADs (n=188)

KRAS mut. subtype	No. (%)	Age, years	Sex	Smoking status
		Median (range)	Men/Women	Never/Smoker/Unknown
All	188	68 (28-86)	121/67	41/146/1
G12C	71 (38%)	69 (35-86)	50 (70%)/21 (30%)	10 (14%)/61 (86%)/0
G12V	45 (24%)	69 (28-84)	27 (60%)/18 (40%)	13 (29%)/32 (71%)/0
G12D	43 (23%)	71 (53-83)	25 (58%)/18 (42%)	13 (30%)/29 (67%)/1 (2%)
G12A	15 (8%)	70 (62-80)	11 (73%)/4 (27%)	1 (7%)/14 (93%)/0
Others*	14 (7%)	72 (53-85)	8 (57%)/6 (43%)	4 (29%)/10 (71%)/0

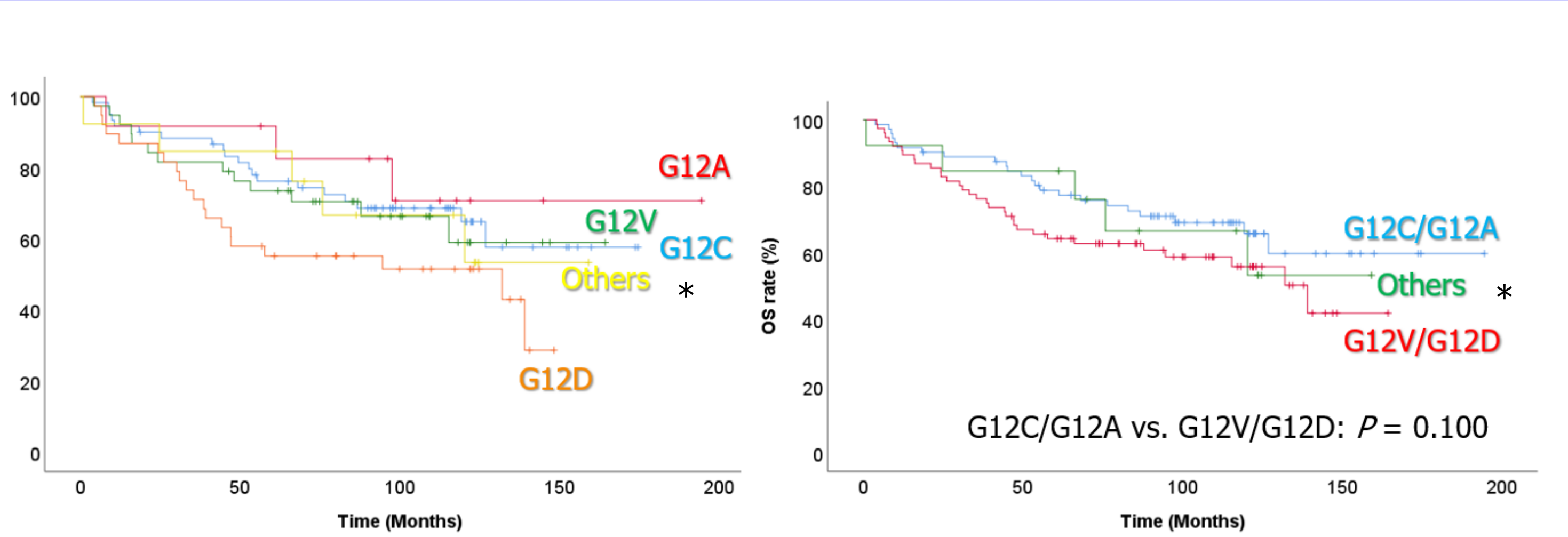
* G13D, G12S, G12F, G12R, G13C, G13Y

Co-occurring mutations according to KRAS mutation subtypes* (n=132)

KRAS mut. subtype	NGS	Co-mutation	TP53	RBM10	STK11	KEAP1	U2AF1	ADIDIA	KMT2D
All	132	76	22	20	7	6	6	5	5
G12C	36	27	12	12	2	2	4	4	3
G12V	19	9	2	3	2	1	0	1	0
G12D	29	12	4	3	1	0	2	0	1
G12A	8	6	2	2	1	2	0	0	1
Others*	5	3	2	0	1	1	0	0	0

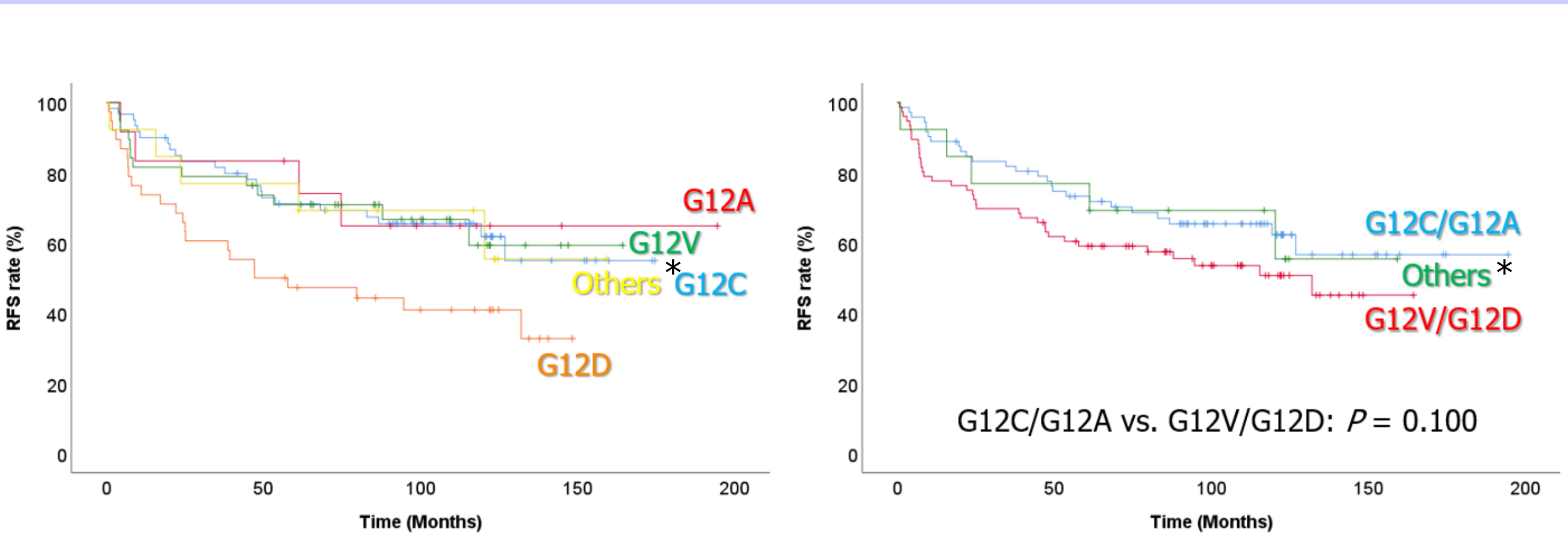
* G13D, G12S, G12F, G12R, G13C, G13Y

Overall survival



* G13D, G12S, G12F, G12R, G13C, G13Y

Relapse-free survival



* G13D, G12S, G12F, G12R, G13C, G13Y

Pathological characteristics according to KRAS mutation subtypes of LUADs (n=188)

KRAS mut. subtype	No. (%)	P-stage			Histological subtype						
		I/II-IV	AIS	MIA	Lepidic	Papillary	Acinar	Solid	IMA	Micro papillary	Enteric
All	188	135/53	4	9	39	31	37	29	37	1	1
G12C	71 (38%)	54/17	2	4	19	9	17	15	4	1	0
G12V	45 (24%)	33/12	1	2	8	7	8	3	15	0	1
G12D	43 (23%)	24/19	0	1	6	7	9	6	14	0	0
G12A	15 (8%)	10/5	0	1	2	5	2	2	3	0	0
Others*	14 (7%)	14/0	1	1	4	3	1	3	1	0	0

* G13D, G12S, G12F, G12R, G13C, G13Y

**PD-L1/PD-L2 expression according to
KRAS mutation subtypes of LUADs (n=158/156)**

KRAS mut. subtype	PD-L1 expression (TPS)				PD-L2 expression (TPS)			
	Total	< 1%	1–49%	50% ≤	Total	< 1%	1–49%	50% ≤
All	158	88 (56%)	40 (25%)	30 (19%)	156	77 (49%)	47 (30%)	32 (21%)
G12C	56	23 (41%)	16 (29%)	17 (30%)	56	31 (55%)	19 (34%)	6 (11%)
G12V	37	28 (76%)	7 (19%)	2 (5%)	37	15 (41%)	8 (22%)	14 (38%)
G12D	38	26 (68%)	9 (24%)	3 (8%)	36	16 (44%)	10 (28%)	10 (28%)
G12A	14	5 (36%)	5 (36%)	4 (29%)	14	7 (50%)	6 (43%)	1 (7%)
Others*	13	6 (46%)	3 (23%)	4 (31%)	13	8 (62%)	4 (31%)	1 (8%)

* G13D, G12S, G12F, G12R, G13C, G13Y

TTF-1 expression according to KRAS mutation subtypes of LUADs (n=157)

KRAS mut. subtype	TTF-1 expression		
	Total	negative	positive
All	157	47 (30%)	110 (70%)
G12C	56	5 (9%)	51 (91%)
G12V	37	18 (49%)	19 (51%)
G12D	37	18 (49%)	19 (51%)
G12A	14	3 (21%)	11 (79%)
Others*	13	2 (15%)	11 (85%)

* G13D, G12S, G12F, G12R, G13C, G13Y

Conclusions

- ✓ KRAS-mutated LUADs have distinct biological characteristics based on mutation subtypes and are different between LUADs with G12C/G12A and G12V/G12D mutations.

- ✓ Therefore, stratification according to KRAS mutation subtype should be considered in designing future clinical trials for new personalized treatments.