

## Supplementary contents

**Table S1.** Clinical Characteristics of Patients Receiving ICI Monotherapy as Second-Line or Later-Line Treatment

**Table S2.** Univariate analysis of the predictive factors of PFS in patients with AGA mutations

**Table S3.** Multivariate Analyses of the Predictive Factors of PFS in Patients With AGA Mutations (*EGFR*, *KRAS*, *HER2*, and *MET* subgroups)

**Table S4. PFS analysis of PD-L1 expression in patients with AGA mutations (*EGFR*, *KRAS*, *HER2*, and *MET* subgroups).**

**Figure S1.** Patient flow diagram

**Figure S2.** *KRAS* subtypes (A) Frequency rate of *KRAS* subtypes (B) mPFS per *KRAS* subtype.  
PFS, progression-free survival

**Table S1.** Clinical characteristics of patients receiving ICI monotherapy as second-line or later-line treatment.

AGA type n (%)		AGA n = 324	Wild Type n = 602	<i>p</i>
Demographic data				
Age	Median age (95% range) (years)	63.1 (39.3-81.7)	66.9 (44.8-82.4)	
	<65	183 (56.5)	234 (38.9)	<0.001
	≥65	141 (43.5)	368 (61.1)	
Sex (n)	Male	172 (53.1)	527 (87.5)	<0.001
	Female	152 (46.9)	75 (12.5)	
Smoking	Never	174 (53.7)	105 (17.4)	<0.001
	Ex or Current	150 (46.3)	497 (82.6)	
ECOG	0-1	315 (97.2)	584 (97.0)	1.0
	≥2	9 (2.8)	18 (3.0)	
Histology	Non-squamous	290 (89.5)	313 (52.0)	<0.001
	Others	34 (10.5)	288 (47.8)	
<b><u>Line of Therapy</u></b>	<b><u>2nd line</u></b>	<b><u>153 (47.2)</u></b>	<b><u>524 (87.0)</u></b>	<b><u>&lt;0.001</u></b>
	<b><u>Later line</u></b>	<b><u>171 (52.8)</u></b>	<b><u>78 (13.0)</u></b>	
Concomitant disease & therapy				
HTN	No	193 (59.6)	345 (57.3)	0.8
	Yes	129 (39.8)	253 (42.0)	
	NI	2 (0.6)	7 (1.2)	
DM	No	244 (75.3)	443 (73.6)	0.6
	Yes	79 (24.4)	154 (25.6)	
	NI	1 (0.3)	5 (0.8)	
RT	No	280 (86.4)	453 (75.2)	<0.001
	Yes	44 (13.6)	149 (24.8)	
Steroid †	No	248 (76.5)	479 (79.6)	0.3
	Yes	76 (23.5)	123 (20.4)	
Antibiotics§	No	273 (84.3)	495 (82.2)	0.5
	Yes	51 (15.7)	107 (17.8)	

Note: Values are shown as number (%) unless indicated otherwise.

\* including crt; † steroid use to treat irAE during ICI therapy; § antibiotic use during ICI therapy; ICI, immune checkpoint inhibitor; AGA, actionable genetic alteration; ECOG, Eastern Cooperative Oncology Group performance status; HTN, hypertension; DM, diabetes mellitus; RT, radiotherapy.

1 **Table S2.** Univariate analysis of the predictive factors of PFS in patients with AGA mutations.

Biomarkers	AGA		EGFR		KRAS		HER2		MET		ALK		BRAF		ROS1		RET	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (≥65, vs <65 )	0.76 (0.60-0.96)	0.02	0.72 (0.50-1.01)	0.1	0.71 (0.43-1.20)	0.21	0.90 (0.43-1.87)	0.78	0.65 (0.28-1.51)	0.32	0.15 (0.02-1.22)	0.08	4.11 (.66-25.79)	0.13	NC		0.76 (0.14-4.20)	0.75
Gender (Female, vs Male)	1.20 (0.95-1.51)	0.13	0.94 (0.67-1.32)	0.7	1.40 (0.84-2.35)	0.20	1.19 (0.55-2.59)	0.66	1.57 (0.64-3.88)	0.98	0.73 (0.18-3.05)	0.67	1.26 (0.28-5.73)	0.76	1.25 (0.24-6.63)	0.79	NC	
Smoking (yes, vs no)	0.84 (0.66-1.06)	0.14	0.96 (0.68-1.36)	0.8	0.65 (0.39-1.09)	0.10	1.07 (0.49-2.35)	0.86	0.84 (0.36-1.94)	0.68	0.92 (0.25-3.48)	0.91	1.73 (0.38-7.79)	0.48	0.70 (0.08-6.02)	0.75	NC	
ECOG ( ≥2, vs 0-1)	1.58 (0.81-3.06)	0.18	2.14 (0.53-8.70)	0.3	2.54 (1.00-6.44)	0.05	1.48 (0.20-11.03)	0.70	0.85 (0.11-6.34)	0.87	NC		NC		NC		NC	
Histology (non-squamous vs. others)	1.22 (0.83-1.79)	0.32	2.05 (0.99-4.23)	0.05	0.85 (0.36-1.98)	0.71	0.76 (0.32-1.81)	0.54	1.36 (0.46-4.03)	0.58	1.85 (0.23-15.06)	0.57	0.85 (0.36-1.98)	0.71	NC		0.75 (0.08-6.73)	0.79
HTN (yes, vs no)	1.00 (0.98-1.01)	0.89	1.00 (0.98-1.02)	0.8	0.65 (0.38-1.11)	0.11	1.46 (0.66-3.20)	0.35	1.00 (0.98-1.02)	0.81	0.51 (0.11-2.46)	0.40	2.98 (0.54-16.39)	0.21	0.90 (0.22-3.66)	0.88	0.89 (0.18-4.47)	0.89
DM (yes, vs no)	1.00 (0.98-1.02)	0.72	1.06 (0.71-1.59)	0.8	1.07 (0.58-2.00)	0.83	1.76 (0.82-3.75)	0.15	1.00 (0.98-1.02)	0.81	2.46 (0.55-11.02)	0.24	1.57 (0.35-7.11)	0.56	NC		NC	
RT (yes, vs no)	1.38 (1.00-1.91)	0.05	0.87 (0.53-1.44)	0.6	1.73 (0.82-3.66)	0.15	1.45 (0.66-3.21)	0.35	NC		3.73 (0.66-20.89)	0.14	NC		0.34 (0.04-2.87)	0.32	1.34 (0.15-12.1)	0.79
Steroid † (yes, vs no)	0.62 (0.46-0.83)	0.001	0.73 (0.49-1.09)	0.1	0.34 (0.17-0.69)	0.003	0.38 (0.15-0.95)	0.04	0.31 (0.07-1.30)	0.11	1.51 (0.40-5.65)	0.54	NC		1.17 (0.22-6.05)	0.86	1.34 (0.15-12.1)	0.79
antibiotics§ (yes, vs no)	0.68 (0.49-0.94)	0.02	0.68 (0.43-1.08)	0.1	0.51 (0.26-1.01)	0.054	0.74 (0.18-3.17)	0.70	0.60 (0.14-2.57)	0.49	1.39 (0.37-5.24)	0.63	NC		NC		1.34 (0.15-12.1)	0.79
PD-L1 cutoff 1% (High, vs Low)	0.62 (0.48-0.80)	0.0002	NC	0.2	0.38 (0.22-0.65)	<0.001	0.55 (0.25-1.24)	0.15	0.54 (0.22-1.34)	0.19	3.22 (0.39-26.33)	0.28	0.24 (0.04-1.53)	0.13	1.44 (0.28-7.32)	0.66	NC	
TMB cutoff 10 (High, vs Low)	0.91 (0.54-1.52)	0.71	0.73 (0.28-1.90)	0.5	0.52 (0.17-1.59)	0.25	0.45 (0.14-1.44)	0.18	NC		NC		NC		NC		NC	
TP53 (mutation, vs wild type)	0.95 (0.69-1.29)	0.72	0.66 (0.33-1.31)	0.2	0.75 (0.44-1.25)	0.27	0.67 (0.30-1.49)	0.33	2.50 (0.68-9.12)	0.17	NC		1.87 (0.31-11.34)	0.49	NC		0.69 (0.11-4.17)	0.68
STK11 (mutation, vs wild type)	1.66 (1.00-2.45)	0.05	1.54 (0.37-6.43)	0.6	3.00 (1.53-5.90)	0.001	NC		1.29 (0.17-9.98)	0.81	NC		1.78 (0.18-17.23)	0.62	NC		NC	
KEAP1 (mutation, vs wild type)	1.40 (0.76-2.58)	0.28	5.47 (0.71-42.00)	0.1	1.85 (0.79-4.33)	0.15	0.66 (0.19-2.21)	0.50	5.15 (0.62-2.88)	0.13	NC		NC		NC		NC	

2 † steroid use to treat irAE during ICI therapy; § antibiotic use during ICI therapy; NC, not calculable; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative  
3 Oncology Group performance status; HTN, hypertension; DM, diabetes mellitus; RT, Radio therapy; TMB, tumor mutational burden.

4

**Table S3.** Multivariate analyses of the predictive factors of PFS in patients with AGA mutations (*EGFR*, *KRAS*, *HER2*, and *MET* subgroups).

Biomarkers	AGA		KRAS		EGFR		HER2		MET	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Smoking (yes vs no)	1.23 (0.71-2.14)	0.46	0.83 (0.27-2.57)	0.74	NC	NC	0.79 (0.16-4.0)	0.78	0.84 (0.19-3.75)	0.82
Steroid <sup>†</sup> (yes vs no)	0.46 (0.23-0.92)	0.03	0.59 (0.14-2.47)	0.47	2.82 (0.68-11.8)	0.16	0.46 (0.07-3.0)	0.42	0.20 (0.02-1.81)	0.15
Antibiotics <sup>\$</sup> (yes vs no)	0.77 (0.37-1.59)	0.5	0.47 (0.13-1.72)	0.26	0.41 (0.12-1.5)	0.18	NC	NC	2.91 (0.18-46.36)	0.45
PD-L1 cutoff 1% (High vs Low)	0.41 (0.25-0.68)	<0.001	0.21 (0.07-0.64)	0.01	NC	NC	0.30 (0.04-2.2)	0.23	0.17 (0.03-0.89)	0.04
TMB cutoff 10 (High vs Low)	1.19 (0.67-2.10)	0.55	0.75 (0.14-3.40)	0.74	1.00 (0.37-2.7)	0.99	0.55 (0.09-3.2)	0.51	NC	NC
TP53 (mutation vs WT)	1.00 (0.61-1.63)	0.99	1.24 (0.41-3.75)	0.70	NC	NC	0.41 (0.07-2.4)	0.33	9.78 (1.22-78.11)	0.03
STK11 (mutation vs WT)	2.25 (0.87-5.83)	0.10	4.53 (1.05-19.47)	0.04	NC	NC	NC	NC	NC	NC
KEAP1 (mutation vs WT)	1.48 (0.63-3.45)	0.37	2.13 (0.49-9.27)	0.32	NC	NC	1.32 (0.08-22.8)	0.85	NC	NC

5

Note: Values are shown as number (%) unless indicated otherwise.

6

<sup>†</sup> steroid use to treat irAE during ICI therapy; <sup>\$</sup> antibiotic use during ICI therapy; PFS, progression-free survival; AGA, actionable

7

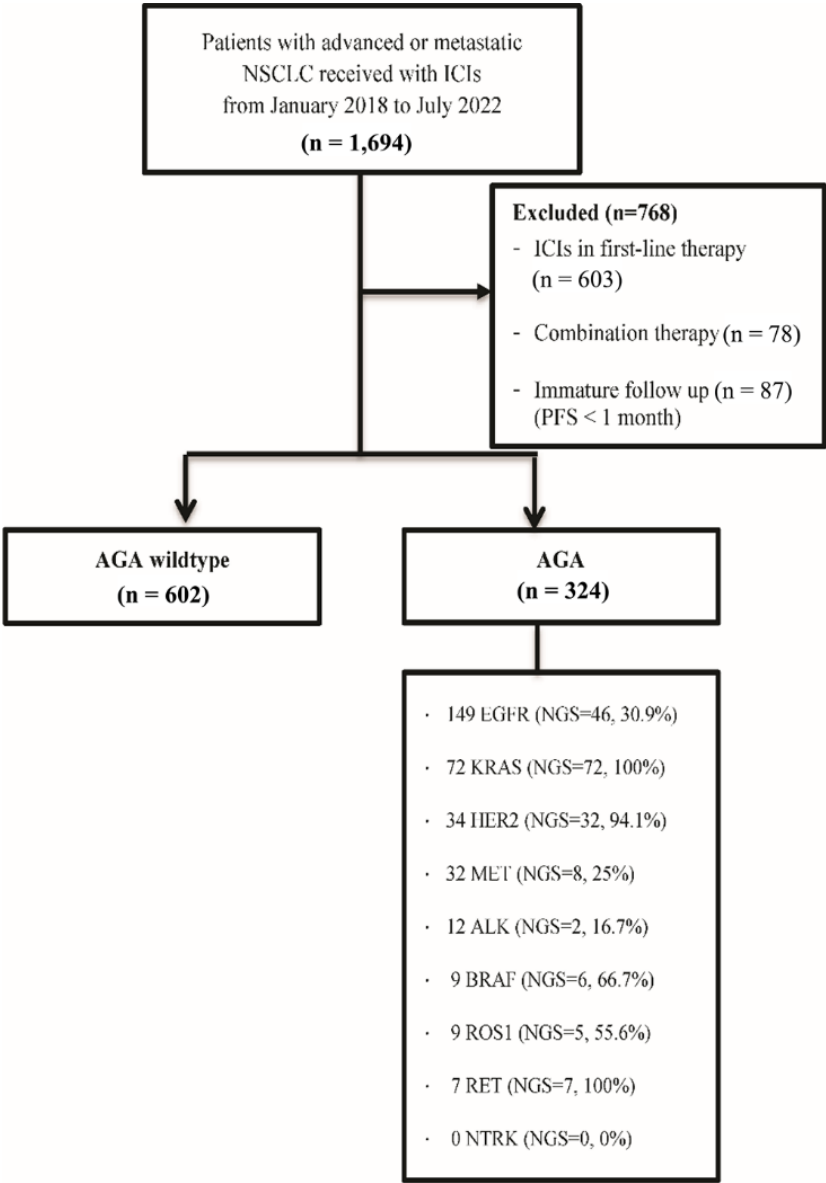
genetic alteration; HR, hazard ratio; CI, confidence interval; TMB, tumor mutational burden. NC, not calculable;

8 **Table S4. PFS analysis of PD-L1 expression in patients with AGA mutations (*EGFR*, *KRAS*, *HER2*, and *MET* subgroups).**

Survival Analysis		AGA n=324			KRAS n=72			EGFR n=149			HER2 n=34			MET n=32		
		PFS			PFS			PFS			PFS			PFS		
		n (%)	median (95%CI)	p	n (%)	median (95%CI)	p	n (%)	median (95%CI)	p	n (%)	median (95%CI)	p	n (%)	median (95%CI)	p
Clinical factor		324			72			149			34			32		
PD-L1 expression		T			72			145			33			31		
cutoff 1%	H (≥1%)	205 (64.7)	2.0 (2.0-3.0)	<0.001	46 (63.9)	4.0 (2.1-6.1)	<0.001	93 (64.1)	2.0 (2.0-2.0)	0.2	14 (42.4)	2.0 (2.0-NR)	0.1	23 (74.2)	5.1 (2.0-NR)	0.2
	L (<1%)	112 (35.3)	2.0 (2.0-2.0)		26 (36.1)	2.0 (1.0-3.0)		52 (35.9)	2.0 (2.0-2.0)		19 (57.6)	2.0 (1.0-3.0)		8 (25.8)	2.5 (1.0-NR)	

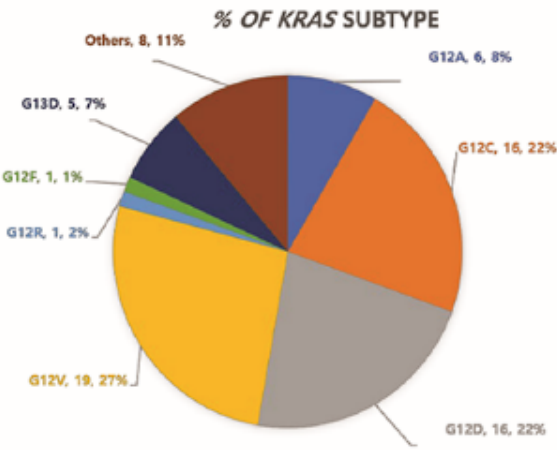
Note: Values are shown as number (%) unless indicated otherwise.

PFS, progression free survival; AGA, actionable genetic alteration; CI, confidence interval. H, High; L, Low NR, not reached.

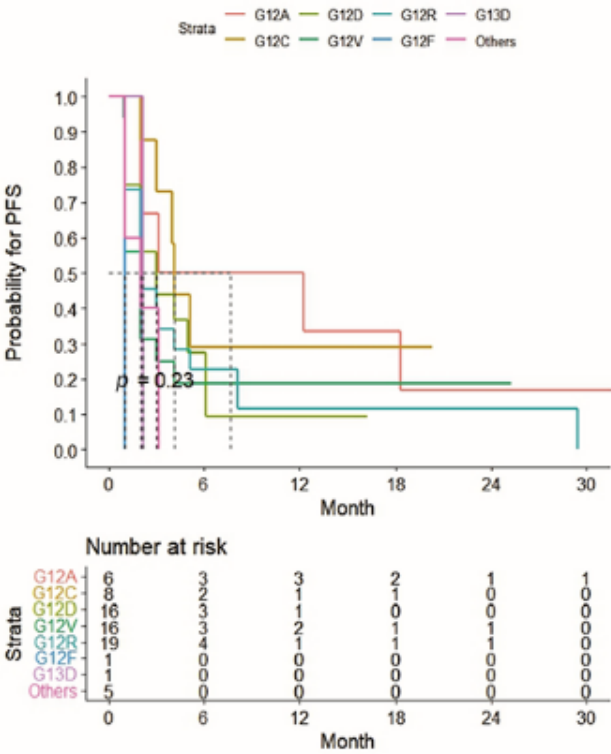


13 **Figure S1.** Patient flow diagram

(A)Frequency rate of KRAS subtypes



(B) mPFS per KRAS subtype



14

15 **Figure S2.** KRAS subtypes (A) Frequency rate of KRAS subtypes (B) mPFS per KRAS subtype.

16 PFS, progression-free survival